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Transtorno de Déficit de Atenção/Hiperatividade em Crianças Muito Prematuras e/ou com Muito Baixo Peso ao Nascer: Avaliação da Prevalência e Desenvolvimento de uma Calculadora de Risco

Porto Alegre, 2020

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Tese apresentada como requisito parcial para obtenção de título de Doutor em Psiquiatria à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento.

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Porto Alegre, ... de ..... de 2020.

A comissão Examinadora, abaixo assinada, aprova a Tese “Fatores de Risco para Transtorno de Déficit de Atenção/Hiperatividade em Crianças Muito Prematuras e/ou com Muito Baixo Peso ao Nascer”, elaborada por Adelar Pedro Franz como requisito parcial para a obtenção do grau de Doutor em Psiquiatria e Ciências do Comportamento.

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“A tarefa
não é tanto ver
aquilo que ninguém viu,
mas pensar
o que ninguém ainda pensou
sobre aquilo
que todo mundo vê.”

Arthur Schopenhauer.

A minha família e, especialmente a minha esposa.

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Aos meus futuros filhos que, embora ainda nem projetados, já têm uma probabilidade predita de 100% de receberem amor, dedicação e cuidado.

SUMÁRIO

ABREVIATURAS E SIGLAS

AIG	Adequado para a Idade Gestacional
AUC	Area Under the Curve
CBCL	Child Behavior Checklist
CPAP	Continuous Positive Airway Pressure
DP	Desvio Padrão
DSM-5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders fourth edition
EP	Extremamente Prematuro
EUA	Estados Unidos da América
GIG	Grande para a Idade Gestacional
HCPA	Hospital de Clínicas de Porto Alegre
HR	Hazard Ratio
IC	Intervalo de Confiança
MBPN	Muito Baixo Peso ao Nascer
MP	Muito Prematuro
OMS	Organização Mundial da Saúde
OR	Odds Ratio
PIG	Pequeno para a Idade Gestacional
ProDAH	Programa de Transtornos de Déficit de Atenção e Hiperatividade
QI	Quociente de Inteligência
RC	Razão de Chance
SDQ	Strengths and Difficulties Questionnaire
TDAH	Transtorno de Déficit de Atenção/Hiperatividade
UFRGS	Universidade Federal do Rio Grande do Sul

LISTA DE SÍMBOLOS

%	Porcentagem
<	Maior que
=	Igual a
>	Menor que
cm	Centímetro
d	Tamanho de efeito d de Cohen
g	Grama
Kg	Quilograma
r	Coeficiente de correlação de Pearson
t	Teste t de Student

RESUMO

A incidência de nascimento prematuro e de baixo peso ao nascer permanece alta em todo o mundo. Além de uma alta taxa de mortalidade, os sobreviventes podem enfrentar muitas morbidades ao longo da vida, como transtornos motores, sensoriais, cognitivos e psiquiátricos, especialmente os recém-nascidos muito prematuros (MP) e os de muito baixo peso (MBPN). O transtorno de déficit de atenção/hiperatividade (TDAH), um transtorno psiquiátrico com alta prevalência, morbidade e custos em saúde, é um dos problemas do neurodesenvolvimento mais comuns descritos nessa população. Embora os recém-nascidos MP/MBPN pareçam ter maior risco futuro de TDAH, a magnitude desse risco não está bem definida. Além disso, vários fatores de risco pré-natais e neonatais podem desempenhar um papel significativo na associação ou etiologia do TDAH em indivíduos MP/MBPN. O objetivo desta tese de doutorado é de revisar sistematicamente e meta-analisar o risco de indivíduos MP/MBPN de desenvolver tanto TDAH como apresentarem uma sintomatologia dimensional do transtorno em comparação com controles com idade e/ou peso de nascimento normais. Buscou-se também desenvolver um modelo preditivo multivariável e criar uma calculadora de risco individualizada para ajudar os médicos a identificar, entre os recém-nascidos MP/MBPN, aqueles com maior probabilidade de ter TDAH no futuro usando preditores rotineiramente coletados nas unidades de terapia intensiva neonatal. No primeiro artigo, em uma revisão sistemática e meta-análise de doze estudos (n=1.787), mostrou-se que tanto os sujeitos MP/MBPN quanto os extremamente prematuros/extremamente baixo peso ao nascer (EP/EBPN) apresentam maior risco de TDAH [Razão de Chances (RC): 3,04; IC 95%, 2,19–4,21]. As análises de subgrupos demonstraram que, quanto mais extremos os casos, maiores as RC (MP/MBPN, RC: 2,25; IC 95%, 1,56–3,26; EP/EBPN, RC: 4,05; IC 95%, 2,38–6,87). Concluímos que os indivíduos MP/MBPN têm um risco aumentado de diagnóstico de TDAH em comparação com os controles, e esses achados são ainda mais fortes no grupo EP/EBPN. Por fim, no segundo artigo, construímos um escore de risco e uma calculadora de risco para o TDAH, com base em sete fatores de risco avaliados em uma coorte clínica de 104 crianças MP/MBPN (sepse tardia confirmada por hemocultura, enterocolite necrosante, convulsões neonatais,

leucomalácia periventricular, síndrome do desconforto respiratório, tempo de internação e número total de sintomas de TDAH da mãe). A calculadora, disponível em https://jscalc.io/calc/unaQG5TuvzVzuzmV, apresentou bons parâmetros de desempenho e é uma ferramenta clínica prática potencial para a identificação precoce de crianças MP/MBPN com alto risco de diagnóstico futuro de TDAH. A presente tese de doutorado trouxe elementos para o dimensionamento da associação entre MP/MBPN e TDAH e constatou quais fatores de risco podem predizer um futuro diagnóstico de TDAH.

Palavras-chave: Nascimento Muito Prematuro. Muito Baixo Peso ao Nascer. Transtorno de Déficit de Atenção/Hiperatividade. Meta-análise. Prognóstico.

ABSTRACT

The incidence of preterm birth and low birth weight remains high worldwide. Besides a high mortality rate, survivors can face many lifelong morbidities, such as motor, sensorial, cognitive, and psychiatric disorders, especially very preterm (VP) and very low birth weight (VLBW) newborns. Attention-deficit/hyperactivity disorder (ADHD), a psychiatric disorder with high prevalence, morbidity, and health costs, is one of the most common neurodevelopmental disorders described in this population. Although VP/VLBW newborns seem to have a higher risk of later ADHD, the magnitude of the risk is not well-defined. Also, several pre-/perinatal risk factors may play a significant role in the association or etiology of ADHD in VP/VLBW individuals. The purpose of this doctoral thesis was to systematically review and meta-analyze the risk of VP/VLBW individuals to develop ADHD categorical diagnosis/dimensional symptomatology compared to controls with normal birth age and/or weight. In addition, we sought to develop a multivariable predictive model and to build an individualized risk calculator to help clinicians to identify, among VP/VLBW newborns, those who are most likely to have ADHD in the future using predictors that are routinely collected in neonatal intensive care unit setting. In the first article, in a systematic review and meta-analysis of twelve studies (n=1,787), we showed that both VP/VLBW and extremely preterm/extremely low birth weight (EP/ELBW) subjects have a higher risk of developing ADHD [odds ratio (OR): 3.04; 95% CI, 2.19–4.21]. Subgroup analyses demonstrated that the more extreme the cases, the higher the ORs (VP/VLBW, OR: 2.25; 95% CI, 1.56–3.26; EP/ELBW, OR: 4.05; 95% CI, 2.38–6.87). We concluded that VP/VLBW subjects have an increased risk of ADHD diagnosis compared to controls and these findings are even stronger in the EP/ELBW group. Finally, in the second article, we built a risk score and a risk calculator for ADHD based on seven risk factors assessed in a clinical cohort of 104 VP/VLBW children (late-onset sepsis confirmed by blood culture, necrotizing enterocolitis, neonatal seizures, periventricular leukomalacia, respiratory distress syndrome, length of hospital stay and total number of maternal ADHD symptoms). The calculator, available at https://jscalc.io/calc/unaQG5TuvzVzuzmV, showed good performance parameters and is a potential practical clinical tool for early identification of VP/VLBW children at

high risk of future ADHD diagnosis. The present doctoral thesis shed light on the magnitude of the association between VP/VLBW children and ADHD and found which risk factors can predict future ADHD diagnosis.

Keywords: Very Preterm Birth. Very Low Birth Weight. Attention-Deficit/Hyperactivity Disorder. Meta-analysis. Prognosis.

APRESENTAÇÃO

Esta tese de doutorado se intitula “Transtorno de Déficit de Atenção/Hiperatividade em Crianças Muito Prematuras e/ou com Muito Baixo Peso ao Nascer: Avaliação da Prevalência e Desenvolvimento de uma Calculadora de Risco”, sendo apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul em 14 de fevereiro de 2020.

Os estudos desenvolvidos nesta tese são resultado de uma parceria entre o Programa de Transtornos de Déficit de Atenção/Hiperatividade (ProDAH) vinculado ao Serviço de Psiquiatria da Infância e da Adolescência e ao Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA) – Universidade Federal do Rio Grande do Sul (UFRGS) e a Unidade de Internação Neonatal e Ambulatório do Serviço de Neonatologia do HCPA – Seguimento de Prematuros.

A motivação inicial para o desenvolvimento desta tese partiu da curiosidade acerca dos desfechos comportamentais nas crianças que nasceram muito prematuras (MP) ou com muito baixo peso ao nascer (MBPN). Apesar da redução da mortalidade destas crianças no período neonatal, há relatos de alta incidência de morbidades crônicas entre os sobreviventes, com destaque para os transtornos do neurodesenvolvimento e, em particular, para problemas comportamentais, como o transtorno de déficit de atenção/hiperatividade (TDAH). O contato na prática clínica com essas crianças e com o sofrimento dos seus pais despertaram meu interesse em contribuir com a produção de conhecimento científico na área, um caminho necessário para a melhoria da assistência destes pacientes.

Considerando-se esta possível relação entre prematuridade e o desenvolvimento de TDAH, nossa questão de pesquisa focou-se na investigação da associação entre estas patologias e na tentativa de ampliar o conhecimento acerca dos possíveis fatores relacionados à prematuridade/baixo peso ao nascer que pudessem estar mediando esta associação e, através destes fatores, poder identificar precocemente os recém-nascidos MP/MBPN que tivessem maior risco de desenvolver TDAH.

Desse modo, o primeiro estudo consistiu em uma revisão sistemática da literatura e meta-análise que teve por objetivo avaliar o risco de crianças que nasceram MP/MBPN de posteriormente desenvolverem TDAH, utilizando-se critérios diagnósticos, tanto categóricos quanto dimensionais bem definidos.

Como foram encontradas associações consistentes entre MP/MBPN e TDAH, o segundo estudo se propôs a avaliar o diagnóstico de TDAH em 104 crianças de aproximadamente 6 anos que nasceram MP/MBPN de uma coorte na unidade de Neonatologia do HCPA, e investigou os fatores de risco perinatais para o desenvolvimento do transtorno, com o intuito de desenvolver uma calculadora de risco para TDAH baseado nestes fatores.

Esta tese está organizada em cinco partes. Na primeira parte, **Introdução**, abordam-se conceitos gerais sobre prematuridade, baixo peso ao nascer e TDAH. A segunda parte, **Revisão de Literatura**, faz-se uma revisão das evidências disponíveis da associação entre estas patologias, das especificidades fenotípicas do TDAH nesta população, dos potenciais mecanismos envolvidos e resume as evidências disponíveis dos fatores de risco para TDAH em indivíduos que nasceram prematuros ou com baixo peso ao nascer. A terceira parte conta com a **Justificativa**, **Objetivos e Considerações Éticas** desta tese. Na quarta parte, encontram-se os textos dos artigos científicos na íntegra: **Artigo 1** (Franz et al., 2018, publicado no *Pediatrics* em 2018) e o **Artigo 2** (pronto para submissão). Na quinta parte, realizam-se as **Considerações Finais**.

1. INTRODUÇÃO

1.1 PREMATURIDADE E BAIXO PESO AO NASCER

1.1.1 Definições:

De acordo com a Organização Mundial da Saúde – (OMS) (1), a Prematuridade é definida pela como o nascimento que ocorre antes de 37 semanas completas de gestação. Pode ser classificada nos seguintes subtipos, de acordo com a idade gestacional de nascimento (2):

- Prematuro: < 37 semanas;
- Muito Prematuro (MP): < 32 semanas;
- Extremo Prematuro (EP): < 28 semanas.

Como a obtenção da idade gestacional necessita da recordação do último período menstrual, de ecografia, ou do exame minucioso do recém-nascido, costuma-se também classificar a prematuridade de acordo com o peso ao nascer, conforme segue (2):

- Baixo Peso ao Nascer: < 2.500 gramas;
- Muito Baixo Peso ao Nascer (MBPN): < 1.500 gramas;
- Extremo Baixo Peso ao Nascer (EBPN): < 1.000 gramas.

A classificação da prematuridade pelo peso ao nascer tem a vantagem de ser de mais fácil obtenção, permanecendo um importante indicador de saúde pública, especialmente em locais onde a avaliação precisa da idade gestacional não é possível (3).

1.1.2 Epidemiologia:

Estima-se que 14,84 milhões de bebês nasceram prematuros em 2014, correspondendo a 10,6% de todos os nascidos vivos em todo o mundo, sendo que as taxas de prevalência podem variar de 8,7% em países europeus a 13,4% no norte da África (4). Mais de 60% dos bebês prematuros nasceram no sul da Ásia e na África

subsaariana, onde 52% dos nascimentos no mundo ocorrem (5). O nascimento prematuro também afeta países ricos. Por exemplo, os Estados Unidos da América (EUA) possuem altas taxas e são um dos dez países com o maior número de nascimentos prematuros. Dos 65 países que possuem dados de tendência temporal estimada, apenas três (Croácia, Equador e Estônia) reduziram as taxas de nascimentos prematuros entre 1990 e 2010 (5).

Apesar de a maioria dos prematuros nascerem próximo das 37 semanas de gestação (84,3% entre a 32ª e 37ª semana de gestação), um número significativo ocorre em faixas mais graves de prematuridade: 10,4% ocorreram entre a 28ª e a 32ª semana, e 5,2% ocorreram antes da 28ª semana (5).

Já a prevalência mundial estimada de baixo peso ao nascer em 2015 foi de 14,6%, correspondendo a 20,5 milhões de nascidos vivos, 91% destes ocorrendo em países de renda baixa e média, principalmente sul da Ásia (48%) e África Subsaariana (24%) (6). Crianças de MBPN correspondem a 1,42% de todos os nascimentos nos EUA em 2015 (7).

A respeito de dados nacionais, o Brasil é o décimo país no mundo com o maior número de nascimentos prematuros (5). Dados de 2017 indicaram que, de cerca de 3 milhões de nascidos vivos desse ano, 319 mil (10,9%) nasceram prematuros. Destes, 45 mil (14,1%) nasceram com menos de 32 semanas (MP). Dos 150 mil que nasceram com baixo peso ao nascer em 2017, 36 mil (24%) tinham menos de 1.500 g (MBPN) (8).

1.1.3 Etiologia:

O nascimento prematuro é uma síndrome com uma variedade de causas que podem ser amplamente classificadas em dois grupos: parto prematuro espontâneo e parto prematuro iniciado pelo profissional (indução do parto ou cesariana eletiva por indicação fetal, materna ou por iatrogenia) (9).

Globalmente, os países que representam a maior carga no número de prematuros têm níveis muito baixos de nascimentos prematuros iniciados pelo profissional, sendo que a maioria dos países africanos tem taxas de cesarianas

inferiores a 5% (10). No entanto, muitos países desenvolvidos e em desenvolvimento apresentam um número cada vez maior de nascimentos prematuros iniciados por profissionais, muitos deles realizados na ausência de uma indicação médica bem definida (11).

O nascimento prematuro espontâneo é um processo complexo, sendo que a causa precisa não é identificada em até metade dos casos (12). A história individual ou familiar de nascimento prematuro é um forte fator de risco (13). Outros fatores incluem idade materna jovem ou avançada, intervalos curtos de gestação, baixo índice de massa corporal materno, gravidez múltipla, doença não transmissível pré-existente, hipertensão na gravidez e infecções (14, 15).

Já os fatores que influenciam especificamente o baixo peso ao nascer são similares, e incluem extremos da idade materna (especialmente menores de 16 anos ou maiores de 40 anos), gravidez múltipla, complicações obstétricas, condições maternas crônicas (por exemplo, transtornos hipertensivos da gravidez), infecções, condições nutricionais, fatores ambientais como poluição do ar em ambientes fechados e uso de tabaco e drogas (16-19).

1.1.4 Mortalidade:

Em países de alta renda, metade dos bebês com menos de 25 semanas têm conseguido sobreviver, mas com evidências crescentes de grande incapacidade (20). Apesar disso, nascimento prematuro e baixo peso ao nascer foram responsáveis por cerca de 17% das mortes de crianças em 2016 nos EUA (21).

Por outro lado, em contextos de baixa e média renda, os prematuros entre 32 e 37 semanas de gestação nem sequer têm cuidados básicos e são responsáveis pela maioria dos bebês prematuros que morrem. Em 2016, as principais causas de morte em crianças menores de 5 anos de idade decorreram de complicações do parto prematuro, representando aproximadamente 16% de todas as mortes, e 35% das mortes entre recém-nascidos (22).

1.1.5 Morbidade:

Mesmo com a alta mortalidade, os avanços no atendimento neonatal de bebês prematuros e de muito baixo peso ao nascer (introdução de aparelhos de *Continuous Positive Airway Pressure* (CPAP), ventilação mecânica, uso de surfactante exógeno, administração rotineira de esteroides pré-natais, evitação de administração crônica pós-natal de esteroides, melhor definição do alvo apropriado para a saturação de oxigênio (23)) aumentaram significativamente as taxas de sobrevivência, principalmente em países desenvolvidos (24). Contudo, as que sobrevivem apresentam risco de desenvolver várias comorbidades (25). A curto prazo, podem apresentar síndrome do desconforto respiratório, retinopatia da prematuridade, displasia broncopulmonar, sepse de início tardio, enterocolite necrosante, hemorragia peri-intraventricular, leucomalácia periventricular, entre outros (26, 27). Já a longo prazo, o risco é o desenvolvimento de uma ampla gama de transtornos do neurodesenvolvimento, incluindo transtornos motores, sensoriais, cognitivos, e o Transtorno de Déficit de Atenção/Hiperatividade (TDAH) (28-30).

Esses riscos de mortalidade e morbidade são maiores para as crianças mais prematuras ou com peso ao nascer mais baixo, como os bebês MP e especialmente para os bebês EP (2, 31, 32).

1.2 TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE

O TDAH é um dos transtornos do neurodesenvolvimento mais comuns na infância e adolescência, caracterizado por um padrão de dificuldade em manter a atenção e/ou por comportamento com excessiva hiperatividade/impulsividade, incompatíveis com a faixa etária (33). Possui uma prevalência mundial estimada de 3.4% [intervalo de confiança de 95% (IC 95%) de 2.6–4.5] entre crianças e adolescentes (34). É um transtorno altamente comórbido com outras patologias psiquiátricas e a persistência dos sintomas até a idade adulta pode ocorrer em aproximadamente 65% dos casos (35).

O TDAH está relacionado a uma série de desfechos adversos na infância, adolescência e na vida adulta, como aumento do risco de lesões (36); aumento da utilização de serviços de saúde (37); mau relacionamento com colegas (38); mau desempenho escolar (39); qualidade de vida pior (40); divórcio (41); acidentes de trânsito (42); desemprego (43); criminalidade (44); maior labilidade emocional, mais neuroticismo, transtornos de ansiedade, transtornos de humor (45); abuso de substâncias (46); suicídio (47) e mortalidade prematura (48); Além disso, o TDAH pode ser um estressor para as famílias pois, além dos resultados adversos acima, as crianças com TDAH tendem a ser mais difíceis de criar (49).

Por fim, o TDAH é um fardo para a sociedade – o custo anual foi estimado entre 143 a 266 bilhões de dólares somente nos EUA, destacando-se os custos de tratamento e educação para crianças, perda de produtividade e renda para adultos, além de altos custos indiretos para as famílias (50).

Em relação à etiologia, há fortes evidências de uma contribuição hereditária para o desenvolvimento do TDAH. Contudo, nem todo risco para o TDAH é genético, e deve-se notar que, além do risco ambiental puro, as estimativas de herdabilidade também incluem um elemento de interação do gene-ambiente (51). Fatores ambientais, responsáveis por 10 a 40% da variação associada ao TDAH (52), são importantes por representarem a parcela potencialmente prevenível do transtorno (53). O grande ônus do TDAH para indivíduos, famílias e sociedade tem levado a um crescente campo de pesquisa sobre fatores de risco ambientais para o TDAH, incluindo a prematuridade e o baixo peso ao nascer.

2. REVISÃO DE LITERATURA

2.1 PREMATURIDADE/BAIXO PESO AO NASCER E TDAH

Nos últimos anos, pesquisas sobre prematuridade e baixo peso ao nascer, através de estudos clínicos e epidemiológicos, têm se dedicado cada vez mais a analisar desfechos neurocomportamentais que ocorrem após o nascimento prematuro e seus respectivos antecedentes e correlatos. Destes, um dos transtornos mais consistentemente encontrado em crianças ou adolescentes que nasceram prematuras ou com baixo peso ao nascer é o TDAH (54, 55). Entretanto, em uma revisão de Sciberras et al. (2017) (51), de todos os fatores de risco pré-natais propostos para o TDAH, nenhum deles pode ser confirmado como causal, incluindo nascimento prematuro e baixo peso ao nascer, pois quanto mais forte era o desenho do estudo, menor a probabilidade de apoiar uma associação.

Até o momento, ainda não foram realizadas meta-análises especificamente projetadas para avaliar a associação entre MP/MBPN e TDAH. Além disso, há muitas limitações nas poucas meta-análises existentes, nas quais os pesquisadores avaliaram associações entre prematuridade ou baixo peso ao nascer e transtornos mais gerais do neurodesenvolvimento.

Em uma meta-análise de 2002 sobre desfechos cognitivos e comportamentais de crianças nascidas prematuras em idade escolar, Bhutta et al. (29) mostraram que crianças nascidas prematuras tinham um risco aumentado em 2,64 vezes para o TDAH (IC 95%, 1,85–3,78) e frequentemente manifestavam sintomas externalizantes quando atingiam a idade escolar. Entretanto essa meta-análise limitou sua busca a estudos de caso-controle e não incluiu artigos que avaliavam crianças com baixo peso ao nascer. Além disso, o pequeno número de estudos incluídos (7 amostras de 6 estudos) tornou seus resultados menos robustos.

Outra meta-análise, de Aarnoudse-Moens et al. (2009) (30) avaliou desempenho acadêmico, problemas comportamentais e função executiva em crianças MP/MBPN. Os autores descobriram que problemas de atenção medidos por pais e professores por meio do *Achenbach's Child Behavior Checklist* e do *Teachers*

Report Form eram mais pronunciados em indivíduos MP/MBPN do que nos controles normais. Eles também encontraram uma forte correlação entre desfechos adversos e nível de maturidade ao nascer: crianças menores e mais prematuras eram mais propensas a ter problemas de comportamento internalizantes, externalizantes, e fraco desempenho acadêmico do que bebês mais pesados e maduros. Entretanto, a pesquisa de artigos foi limitada a um período de 10 anos, o que pode ter excluído estudos relevantes. Os autores observaram que o pequeno número de estudos limitou o poder de algumas análises correlacionais, além de detectarem possível viés de publicação em estudos sobre as classificações dos professores nos problemas comportamentais.

Serati et al. (2017) (56), em uma revisão sistemática da literatura sobre o papel das complicações obstétricas e neonatais no diagnóstico de TDAH na infância, descobriram que o baixo peso ao nascer (tamanho de efeito d de Cohen: 0,31–1,64) e nascimento prematuro (tamanho de efeito d de Cohen: 0,41–0,68) foram os fatores mais importantes associados a um diagnóstico futuro de TDAH. Os autores não encontraram uma relação proporcional clara entre redução de peso e aumento do risco do TDAH para pesos ao nascer abaixo de 2.500 g. Sobre o nascimento prematuro, eles alertaram que diferentes estudos usavam diferentes definições de nascimento prematuro, o que impediu avaliações adicionais.

Momany et al. (2018) (57), em uma meta-análise da associação entre peso ao nascer e sintomas de TDAH, encontraram uma associação pequena, mas significativa. Os indivíduos nascidos com baixo peso ao nascer manifestaram maiores sintomas de TDAH [coeficiente de correlação de Pearson (r): - 0,15]. No entanto, este estudo não foi realizado em MP/MBPN e não avaliou o TDAH do ponto de vista diagnóstico. Verificou-se que tipo de amostra, peso médio de nascimento, região geográfica, informante dos sintomas de TDAH, método de medição de sintomas de TDAH e etnia contribuíram significativamente para a heterogeneidade nos tamanhos dos efeitos.

2.2 ESPECIFICIDADES FENOTÍPICAS DO TDAH EM PREMATUROS

Apesar da falta de evidências consistentes, pesquisadores sugerem que indivíduos nascidos prematuros ou com baixo peso ao nascer que desenvolvem TDAH apresentam especificidades fenotípicas que divergem de indivíduos com TDAH que nasceram a termo e com peso de nascimento normal. Isso inclui: maior prevalência de complicações gestacionais e neonatais (30, 58), menor incidência de comorbidades psiquiátricas (59-61), menor Quociente de Inteligência (QI) e piores parâmetros neuropsicológicos (29, 62-64), maior estabilidade diagnóstica do TDAH da infância até a vida adulta (59, 63), e maior predominância de sintomas de desatenção (54, 55, 60). Além disso, crianças prematuras com TDAH não apresentam o padrão típico (65) de maior prevalência no sexo masculino em comparação ao sexo feminino (59, 61, 66).

2.3 MECANISMOS QUE VINCULAM PREMATURIDADE AO TDAH

2.3.1 Genética

Nas últimas décadas, estudos de famílias, gêmeos e adoção mostram que o TDAH apresenta uma herdabilidade estimada de 74%, o que destaca o papel genético em sua etiologia (67). Vários loci genéticos foram implicados, mas todos com uma contribuição individual pequena para o desenvolvimento de TDAH (67). Cerca de um terço da herdabilidade do TDAH é devida a um componente poligênico que compreende muitas variantes comuns, cada uma contribuindo com um pequeno efeito para o risco de TDAH (67).

Da mesma forma, estima-se que o baixo peso ao nascer tenha uma alta herdabilidade, de aproximadamente 50%, afetando a capacidade de sobrevivência de um feto em desenvolvimento, tanto no útero quanto após o nascimento (68). Também existe agregação familiar no parto prematuro, já que mulheres nascidas prematuramente têm um risco maior de terem parto prematuro, e esse risco aumenta em 80% nas mulheres cujas irmãs tiveram parto prematuro (69).

Apesar destas fortes contribuições genéticas, alguns estudos postulam que a associação entre TDAH e baixo peso ao nascer não parece ser devida a uma

suscetibilidade genética comum (57). Em um estudo utilizando dados da população de gêmeos da Suécia, as associações entre o peso ao nascer e sintomas de TDAH foram semelhantes para gêmeos monozigóticos e dizigóticos. Os autores deste estudo concluíram que existe uma associação independente entre o baixo peso ao nascer e sintomas de TDAH, mesmo após o controle de todos os confundidores ambientais e genéticos compartilhados, sugerindo uma via causal entre peso ao nascimento e TDAH (70). Em um estudo longitudinal de diferenças entre gêmeos, Lim et al. (2018) (71) também apontaram para a natureza causal da associação observada entre peso ao nascer e sintomas de TDAH usando gêmeos monozigóticos para controlar confundidores genéticos e ambientais compartilhados. A associação persistiu desde a infância até a adolescência e foi mais forte e mais persistente para desatenção em comparação com hiperatividade/impulsividade. Achados similares de causalidade também foram encontrados em um estudo utilizando dados longitudinais de gêmeos na Holanda (72).

Entretanto, inferências de causalidade entre prematuridade/baixo peso ao nascer e TDAH ainda não estão totalmente esclarecidas uma vez que fatores genéticos maternos podem estar confundindo esta associação. Mães com alto risco genético para o TDAH também podem estar em risco aumentado para intercorrências adversas durante a gravidez, o que foi evidenciado por Leppert et al. (2019) (73), em um estudo de coorte de base populacional de 7.921 mães. O escore poligênico de risco para TDAH das mães foi associado a uma série de intercorrências gestacionais/neonatais que, por sua vez, estão relacionadas a distúrbios do neurodesenvolvimento, como o TDAH na prole. Já escores poligênicos de risco para outros distúrbios do neurodesenvolvimento, como o transtorno do espectro autista e esquizofrenia mostraram pouca evidência de associação com intercorrências gestacionais/neonatais neste estudo. Os autores deste estudo destacam a necessidade de considerar cuidadosamente possíveis confundidores genéticos e diferentes abordagens ao avaliar os efeitos das intercorrências pré-natais e neonatais nos distúrbios do neurodesenvolvimento dos filhos.

2.3.2 Origem Desenvolvimental

A hipótese das origens desenvolvimentais da saúde e da doença (do inglês "*Developmental Origins of Health and Disease Hypothesis*") pode ajudar a explicar a ligação entre prematuridade/baixo peso ao nascer e TDAH (57). Essa teoria propõe que mudanças no ambiente pré-natal durante períodos sensíveis de desenvolvimento podem resultar em alterações epigenéticas, estruturais ou fisiológicas a longo prazo que, por um lado, "programam" o feto em desenvolvimento a se adaptar às perturbações do ambiente pré-natal, mas deixando-o, por outro lado, mal adaptado para o ambiente pós-natal, e aumentando assim o risco para condições crônicas de saúde como diabetes, doença cardiovascular, asma, câncer, osteoporose e transtornos neuropsiquiátricos (74-78).

2.3.3 Isquemia-Hipóxia

Consistente com a hipótese das origens desenvolvimentais da saúde e da doença, uma revisão recente de Smith et al. (2016) (79) postulou uma via etiológica que liga o peso ao nascer ao TDAH por meio da isquemia-hipóxia pré-natal, que consiste no suprimento insuficiente de sangue e oxigênio no período intrauterino. Conforme revisado nesse artigo, durante eventos prolongados de isquemia-hipóxia pré-natal, ocorre uma expressão gênica alterada no cérebro e nos tecidos periféricos em desenvolvimento e alterações epigenéticas no sentido de se adaptar ao contexto da isquemia-hipóxia e promover sua sobrevivência. Entretanto, essa expressão gênica alterada e as alterações epigenéticas em resposta à isquemia-hipóxia duradoura podem, a longo prazo, aumentar o risco para transtornos do neurodesenvolvimento, como uma vulnerabilidade para o TDAH (79).

2.3.4 Crescimento Compensatório

Outra hipótese levantada para explicar a ligação entre baixo peso ao nascer e TDAH é o crescimento compensatório (80), que consiste no ganho de peso extra nos

primeiros anos de vida, geralmente através de fórmulas nutricionais, para compensar e se igualar ao peso de indivíduos da mesma idade. Apesar dos efeitos positivos, o crescimento compensatório rápido em bebês saudáveis nascidos a termo (com peso normal ou pequeno para a idade gestacional) pode estar associado a efeitos adversos a longo prazo, como obesidade e outras doenças crônicas (80). Entretanto, isso não parece válido para bebês prematuros, que podem obter ganhos posteriores no neurodesenvolvimento com o ganho rápido de peso na infância (80). Adicionalmente, ainda não está claro se esse mecanismo atua no TDAH, já que um estudo realizado por Groen-Blokhuis et al. (2011) (72) não encontrou associação entre crescimento compensatório e futuros problemas de desatenção.

2.3.5 Neuroinflamação

Numa revisão feita por Dunn et al. (2019) (81) sobre neuroinflamação como um fator de risco para TDAH, o autor destaca as seguintes evidências do papel da neuroinflamação na fisiopatologia do TDAH: a) a comorbidade acima do acaso de TDAH com transtornos inflamatórios e autoimunes, b) estudos iniciais indicando uma associação com o TDAH e aumento de citocinas séricas, c) evidências preliminares de estudos genéticos demonstrando associações entre polimorfismos em genes associados às vias inflamatórias e ao TDAH, d) evidências emergentes de que a exposição precoce a fatores ambientais pode aumentar o risco de TDAH por meio de um mecanismo inflamatório e e) evidências de modelos animais de ativação imune materna documentando desfechos comportamentais e neurais consistentes com TDAH.

De fato, a exposição precoce a fatores ambientais pode promover a ativação de células imunes e da microglia (82), causando alterações nas citocinas pró-inflamatórias e anti-inflamatórias, envolvidas no metabolismo do triptofano e nas vias dopaminérgicas envolvidas no TDAH (83, 84). Além disso, sabe-se que o aumento da inflamação durante a gravidez pode ser um dos determinantes do baixo peso ao nascer (85).

2.4 FATORES DE RISCO PARA TDAH EM PREMATUROS

Apesar de uma forte influência genética, diversas morbidades típicas de crianças prematuras ou com baixo peso ao nascer e de suas mães podem exercer um papel significativo no futuro desenvolvimento do TDAH (56). Levando-se em conta a evidência de associação entre prematuridade e o baixo peso ao nascer com TDAH e ao fato de termos uma melhor compreensão dos mecanismos biológicos subjacentes do cérebro em desenvolvimento como potencial fator causal para transtornos neuropsiquiátricos (86), os estudos começaram a investigar o papel dos fatores de risco pré-natais e neonatais desta associação.

2.4.1 Considerações Metodológicas dos Fatores de Risco

Conforme destaca Momany et al. (2018) (57), um grande volume de estudos que avaliam possíveis fatores de risco para TDAH apresentam resultados positivos, mas, de maneira geral, apresentam uma série de limitações metodológicas que devem ser consideradas:

a) Os estudos de desenho caso-controle geralmente são baseados em questionários ou entrevistas com as mães vários anos após o nascimento, com a possibilidade de viés de memória, além de muitas vezes apresentarem amostras relativamente pequenas ou selecionadas.
b) Nos estudos de coorte, o desfecho avaliado tem sido frequentemente sintomas ou comportamentos relacionados ao TDAH em vez do diagnóstico formal. As medidas usadas para avaliar o diagnóstico de TDAH variam de simples autorrelatos, uso ou não de medicação para TDAH, vários tipos de questionários diferentes (muitas vezes só de triagem para o TDAH) e entrevistas que, na maioria das vezes, possuem validade diagnóstica limitada, ou o uso exclusivo de testagens que avaliam as funções neuropsicológicas de atenção.
c) Resultados diferentes de acordo com o tipo de informante (autorrelato, pais, professores, médico).

d) Diferentes definições e pontos de corte utilizados na avaliação dos fatores pré-natais e neonatais.
e) Pouco tempo de seguimento nos estudos de coorte, ou tempos de seguimentos muito variados, dificultando comparações de indivíduos com a mesma idade.
f) Há muita variabilidade empregada nos desenhos dos estudos para investigar o peso ao nascer e os sintomas de TDAH. Alguns estudos dicotomizam indivíduos com base no peso ao nascer, outros com base no status de TDAH, e ainda outros estudos examinam uma ou ambas as variáveis como medidas contínuas.

Levando essas limitações metodológicas em conta, segue uma revisão dos principais fatores de risco pré-natais e neonatais possivelmente associados ao TDAH, com ênfase na população de indivíduos que nasceram prematuros ou com baixo peso ao nascer.

2.4.2 Fatores Maternos:

2.4.2.1 Baixo Nível Socioeconômico

O baixo nível socioeconômico é considerado um fator de risco para problemas atencionais durante a infância entre crianças nascidas prematuras (54, 87, 88). Esta variável relaciona-se com uma variedade de fatores, incluindo etnia, estresse psicossocial e escolaridade maternos (89) e está associada a pior acesso a cuidados pré-natais, pior nutrição e menor peso ao nascer do bebê (90, 91). Larson et al. (2014) (92) mostraram que a baixa renda familiar na primeira infância tinha uma associação dose-dependente com o TDAH, mesmo após o controle de confundidores (RC para o quartil 1: 2,09; IC 95%, 2,00–2,19; quartil 2: 1,36; IC 95%, 1,30–1,42; quartil 3: 1,13; IC 95%, 1,08–1,18).

2.4.2.2 Diabetes Mellitus Materno

Estudos realizados numa coorte (93) de 333.182 nascimentos entre 1995 a 2012 constatou que a gravidade do diabetes materno (diabetes tipo 1 preexistente > diabetes tipo 2 preexistente > diabetes mellitus gestacional requerendo uso de medicamentos antidiabéticos) influencia o risco de TDAH. Em comparação com crianças não expostas ao diabetes materno, as RC ajustadas para TDAH em crianças foram de 1,57 (IC 95%, 1,09–2,25) para exposição ao diabetes tipo 1, 1,43 (IC 95%, 1,29–1,60) para diabetes tipo 2, 1,26 (IC 95%, 1,14–1,41) para diabetes gestacional que requer uso de medicamentos antidiabéticos e 0,93 (IC 95%, 0,86–1,01) para diabetes mellitus gestacional que não requer medicamentos (não significativo). Porém, o risco de TDAH não foi associado ao diabetes mellitus gestacional tomado como um todo (p=0,50).

Uma recente revisão sistemática e meta-análise (94) de 2019 avaliou a associação entre diabetes mellitus parental e risco de TDAH na prole. Com dados de 13 estudos observacionais, contendo 5.052.736 participantes, os pesquisadores descobriram que o diabetes mellitus pré-gestacional materno foi associado a um risco aumentado de TDAH na prole (RC: 1,40; IC 95%, 1,31–1,50) nas análises ajustadas. Também foram observados riscos aumentados de TDAH na prole entre aqueles com diabetes tipo 1 materno preexistente (RC: 1,39; IC 95%, 1,27–1,52) e diabetes tipo 1 paterno (RC: 1,20; IC 95%, 1,13–1,28) nas análises ajustadas.

2.4.2.3 Transtornos Hipertensivos da Gravidez

Os transtornos hipertensivos da gravidez [hipertensão crônica (essencial/secundária), hipertensão do jaleco branco, hipertensão mascarada, hipertensão gestacional transitória, hipertensão gestacional e pré-eclâmpsia] afetam 5% a 15% de todas as gestações e, portanto, estão entre as complicações pré-natais mais comuns (95, 96). Getahun et al. (2013) (97), ao examinarem prontuários de quase 82.000 crianças de 5 a 11 anos, descobriram que crianças expostas a asfixia ao nascimento (Apgar menor que 7 em 5 minutos), síndrome do desconforto respiratório neonatal e pré-eclâmpsia tiveram um risco significativamente maior (26%, 47% e 34%, respectivamente) de TDAH em comparação com crianças não expostas.

Esse risco aumentado permaneceu o mesmo em todos os grupos étnicos. Análises adicionais por idade gestacional revelaram que a pré-eclâmpsia permaneceu um preditor significativo de TDAH, independentemente da idade gestacional no parto. Já a síndrome do desconforto respiratório obteve um risco leve ou ausente de TDAH quando avaliada nas gestações a termo.

Maher et al. (2018) (98), em uma revisão sistemática e meta-análise, concluíram que os filhos expostos a transtornos hipertensivos da gravidez tinham 30% mais chances de ter TDAH em comparação com os filhos não expostos (RC ajustado: 1,29; IC 95%, 1,22–2,36). Examinando a associação entre pré-eclâmpsia e TDAH isoladamente não fez com que a estimativa se alterasse (RC: 1,28; IC 95%, 1,22 – 1,36). As chances de TDAH aumentaram 70% quando foram avaliadas associações com outros transtornos hipertensivos da gravidez (RC: 1,70; IC 95%, 1,06–2,72). No entanto, essa diferença de subgrupo não foi estatisticamente significativa (p=0,24).

Dos possíveis mecanismos propostos para explicar essas associações, o autor (98) hipotetiza que a disfunção placentária, associada a transtornos hipertensivos da gravidez, pode resultar em menor perfusão placentária e estresse oxidativo (99). Por sua vez, a disponibilidade subótima de nutrientes e oxigênio para o feto, atribuível à insuficiência placentária, pode afetar o cérebro em desenvolvimento, aumentando o risco para transtornos do neurodesenvolvimento (100, 101). Böhm et al. (2019) (102) em um estudo avaliando o efeito de transtornos hipertensivos da gravidez no risco de TDAH na prole, cita que as alterações anatômicas descritas em crianças de gestações complicadas por pré-eclâmpsia também foram implicadas no TDAH e especula que a via inflamatória materna pode ser uma das principais candidatas para explicar essas associações.

2.4.2.4 Infecção Materna

Em um estudo realizado por Mann et al. (2011) (103) para investigar a hipótese de que infecção gênito-urinária materna estava associada ao aumento do risco de TDAH, foram coletados dados do *Medicaid* em mulheres grávidas e seus filhos na Carolina do Sul – EUA, nascidos de 1996 a 2002. Com dados de acompanhamento

até 2008, casos de TDAH foram identificados no período escolar com base nos diagnósticos feitos nos arquivos do *Medicaid* da criança. Das 84.721 crianças acessadas, infecção gênito-urinária materna foi associada a chances significativamente aumentadas de TDAH (RC: 1,29; IC 95%, 1,23–1,35). A pré-eclâmpsia também foi associada ao aumento do risco (RC: 1,19; IC 95%, 1,07–1,32). Crianças cujas mães tiveram infecção geniturinária e pré-eclâmpsia tiveram 53% mais chances de ter TDAH, em comparação com aquelas que não tiveram exposição. Quando foram examinamos os diagnósticos específicos, infecção por clamídia/uretrite não-gonocócica, tricomoníase, infecção do trato urinário e candidíase foram associados ao aumento do risco de TDAH, enquanto infecção por gonorreia não evidenciou aumento de risco.

2.4.2.5 Corioamnionite

A corioamnionite, geralmente associada a uma resposta inflamatória fetal, é uma causa comum de parto prematuro (104). Em um estudo gerador de hipóteses (105) com dados de uma coorte de nascimentos de Boston – EUA, a corioamnionite histológica placentária e o nascimento prematuro aumentaram de maneira aditiva as chances de TDAH (RC ajustada: 2,75; IC 95%, 1,55–4,90). Essa associação foi mais pronunciada quando o parto prematuro foi espontâneo do que no parto prematuro clinicamente indicado. O parto prematuro isolado, na ausência de corioamnionite, teve apenas uma associação moderada com o TDAH.

2.4.3 Fatores Neonatais:

2.4.3.1 Sexo

Estudos que examinaram o sexo como moderador da associação entre peso ao nascer e sintomas de TDAH produziram resultados conflitantes, conforme segue.

Um estudo de Ask et al. (2018) (106) investigou se o sexo moderava a associação entre idade gestacional ao nascer e sintomas de TDAH em crianças com

5 anos de idade. Após o ajuste para fatores genéticos e ambientais, as crianças nascidas prematuras tiveram uma pontuação média 0,24 desvios padrão (DP) (IC 95%, 0,14–0,34) maior nos testes de sintomas de TDAH, em comparação com crianças nascidas na semana gestacional 40. O sexo moderou a associação da idade gestacional com os sintomas do TDAH e a associação pareceu ser mais forte entre as meninas, sugerindo que as consequências negativas do nascimento prematuro foram mais pronunciadas nas meninas. Eles comentaram que uma pontuação alta em desatenção pode ser um reflexo de construtos relacionados como, por exemplo, de ansiedade, que é mais prevalente entre meninas do que meninos, uma possível explicação para a diferença de sexos observada.

Um estudo de Murray et al. (2015) (107) identificou que nas meninas, as dificuldades de atenção estavam associadas a ser Pequeno para Idade Gestacional (PIG, peso ao nascer abaixo do percentil 10), circunferência da cabeça menor, baixo índice ponderal e baixo peso ao nascer em modelos não ajustados (RC para baixo peso: 1,65; IC 95%, 1,26–2,17, p<0,001), mas nenhuma dessas associações foi identificada em meninos. Os autores concluíram que meninas com crescimento fetal prejudicado podem ser mais vulneráveis a certos ambientes intrauterinos subótimos, que aumentam o risco de dificuldades de atenção na infância.

Já Momany et al. (2017) (108) examinou associações entre peso ao nascer e TDAH, e até que ponto essa associação foi moderada pelo sexo. O peso ao nascer previu significativamente o TDAH, e o baixo peso ao nascer associou-se a maior taxa de TDAH nos homens, mas não nas mulheres. Os resultados permaneceram inalterados quando controlados para uma série de confundidores, incluindo idade dos pais, uso de tabaco na gestação, psicopatologia comórbida, além de outros indicadores de saúde materno-infantil durante o período pré-natal e neonatal. Martel et al. (2013) (109) propôs que a Teoria da Seleção Sexual poderia explicar por que os homens têm um risco aumentado de desenvolver TDAH após a exposição a fatores de risco no início da vida, como o baixo peso ao nascer. A hipótese é de que a desinibição e a busca por sensações podem ser importantes marcadores de risco para transtornos externalizantes de início na infância em homens. A teoria sugere que essa maior vulnerabilidade em homens pode ser um produto de sua maior exposição à

testosterona pré-natal, o que os torna mais suscetíveis a estressores pré-natais que prejudicam a neurotransmissão dopaminérgica, especialmente para aqueles com alelos genéticos associados à função dopaminérgica mais baixa.

2.4.3.2 Pontuações de Apgar

Um estudo de base populacional mostrou que, além do nascimento prematuro e do baixo peso ao nascer, baixos índices de Apgar, fenda oral e epilepsia materna aumentam o risco de TDAH na vida adulta, persistindo até 40 anos após o nascimento (110). Em outro grupo de crianças extremamente prematuras, a medida de Apgar menor do que 8 no quinto minuto foi associada ao uso de medicamentos para tratamento do TDAH (87). Em uma meta-análise de 2016 (111) sobre associação entre hipóxia-isquêmia perinatal e TDAH, incluído 45.821 casos e 9.207.363 controles, constatou que os seguintes fatores estavam associados ao TDAH: pré-eclâmpsia (RC: 1,31; IC 95%, 1,26–1,37), índice de Apgar menor que 7 aos 5 minutos (RC: 1,31; IC 95%, 1,12–1,54), apresentação pélvica/transversal (RC: 1,14; IC 95%, 1,06–1,23) e prolapso de cordão umbilical (RC: 1,10; IC 95%, 1,06–1,15).

2.4.3.3 Hipoglicemia Neonatal

Hipoglicemia neonatal após diabetes gestacional foi associada a déficits de longo prazo na atenção e disfunção cerebral mínima. Num estudo sueco (112), 13 crianças com e 15 sem hipoglicemia neonatal foram investigadas aos 8 anos de idade e foram comparados com 28 controles saudáveis pareados por idade. Crianças com hipoglicemia neonatal apresentaram significativamente mais sintomas de TDAH e disfunção cerebral mínima do que os controles. Quatro filhos de mães diabéticas com hipoglicemia neonatal foram avaliados pelos pais como hiperativas, impulsivas e facilmente distraídas, mas nenhum no grupo controle ($\chi 2$: 10,5; p=0,004). Atividades eletroencefalográficas anormais nas regiões fronto-temporal e fronto-parietal foram observadas nessas crianças, o que é consistente com achados de crianças com TDAH (113).

2.4.3.4 Score for Neonatal Acute Physiology-II (SNAP-II)

O escore SNAP-II consiste em uma pontuação com base em sinais vitais rotineiramente disponíveis e testes laboratoriais obtidos durante as primeiras 12 horas pós-natais (114). Em uma coorte (115) de 874 crianças nascidas antes de 28 semanas de gestação, os escores altos no SNAP-II (⩾30), presentes em 23% dos participantes, foram associados a um risco aumentado de TDAH, tanto pelo relato dos pais (p=0,03) como pelo relato de professores (p=0,003). Eles também encontraram associações com comprometimento cognitivo (QI, função executiva, e linguagem), desfechos neurológicos adversos (epilepsia, função motora grossa prejudicada), disfunção social (transtorno do espectro autista) e adversidades relacionadas à educação (desempenho escolar baixo e necessidade de apoio educacional).

2.4.3.5 Síndrome do Desconforto Respiratório

A síndrome do desconforto respiratório é também conhecida como doença da membrana hialina ou deficiência de surfactante. Getahun et al. (2013) (97), ao examinarem prontuários de quase 82.000 crianças de 5 a 11 anos, descobriram que crianças expostas a asfixia ao nascimento (Apgar menor que 7 em 5 minutos), Síndrome do Desconforto Respiratório neonatal e pré-eclâmpsia tiveram um risco significativamente maior (26%, 47% e 34%, respectivamente) de TDAH em comparação com crianças não expostas. Análises adicionais por idade gestacional revelaram que a pré-eclâmpsia permaneceu um preditor significativo de TDAH, independentemente da idade gestacional no parto. Já a síndrome do desconforto respiratório obteve um risco leve ou ausente de TDAH quando avaliada nas gestações a termo.

Farel et al. (116) avaliaram crianças de MBPN, com e sem doença pulmonar crônica, uma complicação frequente da síndrome do desconforto respiratório e da displasia broncopulmonar. Embora ambos os grupos terem apresentado escores de sintomatologia 1 desvio padrão (DP) abaixo da média na *Conners Hyperactivity Rating*

Scale, não foram encontradas diferenças significativas entre os dois grupos. Já nas testagens neuropsicológicas, crianças com doença pulmonar crônica foram classificadas como tendo um comprometimento atencional significativamente maior (59%) do que as crianças com MBPN sem doença pulmonar crônica (32%).

2.4.3.6 Displasia Broncopulmonar

Ainda há pouca informação disponível sobre problemas comportamentais em crianças com displasia broncopulmonar. Embora sejam necessárias mais pesquisas para determinar o impacto da displasia broncopulmonar nas habilidades de atenção, sabe-se que essa população tende a ter problemas para concentrar e manter a atenção (117).

Um estudo prospectivo realizado por Short et al. (2003) (118) acompanhou crianças com MBPN, com e sem displasia broncopulmonar, e com peso normal ao nascer até os 8 anos de idade. Mais crianças com displasia broncopulmonar receberam o diagnóstico de TDAH do que as crianças com MBPN sem displasia broncopulmonar ou nascidas a termo. Embora os pais e professores não tenham conseguido diferenciar as crianças com displasia broncopulmonar como tendo mais problemas de atenção (pela *Conners Rating Scale*), diferenças significativas foram encontradas nas tarefas de atenção medidas por testagens neuropsicológicas (*Continuous Performance Test*) entre aquelas com displasia broncopulmonar e as nascidas a termo. Os autores sugerem que essa medida de atenção aos 8 anos poderia ser uma indicação precoce de déficits de atenção que poderiam ficar mais evidentes ao longo do tempo. Como várias crianças com displasia broncopulmonar foram incapazes de concluir as testagens neuropsicológicas e como as mesmas não foram realizadas em crianças com escores de QI abaixo de 70, isso pode ter subestimado a gravidade das dificuldades de atenção nessas crianças.

Gray et al. (2007) (119), numa coorte de 78 crianças com displasia broncopulmonar nascidas com 26 a 33 semanas de gestação, encontraram mais problemas internalizantes entre as com displasia broncopulmonar em idade escolar quando comparadas com controles prematuros usando a *Child Behavior Checklist*

(CBCL) preenchida pelos pais. Pouca variação foi encontrada nos escores da *Teacher Report Form* da CBCL entre as crianças prematuras com displasia broncopulmonar. Entretanto, quando as crianças com displasia broncopulmonar foram comparadas com colegas de sala de aula, diferenças significativas foram encontradas em vários aspectos do comportamento, incluindo desatenção (p=0,0001), comportamentos internalizantes (p=0,01), problemas totais (p=0,001), sociais (p=0,047) e de pensamento (p=0,047).

2.4.3.7 Ventilação Mecânica

Apesar de sua função pretendida para proteger o cérebro de hipoxemia e asfixia, a ventilação mecânica pode ter muitos efeitos adversos no cérebro de um bebê prematuro. Destes, podemos citar: o aumento da pressão intracraniana, flutuações nas velocidades de fluxo arterial e venoso cerebrais (120), alteração da hemodinâmica cerebral e da oxigenação devido à aspiração e reposicionamento rotineiro do tubo endotraqueal necessário ao usar um ventilador (121, 122), episódios de hipocapnia e hiperóxia associados a danos cerebrais (123), lesão pulmonar, aumento de citocinas inflamatórias que causam lesões na substância branca (124), entre outros. Tomados em conjunto, todos esses fatores podem contribuir para danos cerebrais difusos e sutis e afetar o processo de maturação cerebral em bebês EBPN, o que poderia levar ao desenvolvimento futuro de TDAH.

Estudos recentes sobre a microestrutura da substância branca em EP constataram que o número de dias em ventilação mecânica foi um fator contribuinte independente para a lesão difusa da substância branca (125, 126), o que já foi relacionado a um aumento na densidade de astrócitos, infiltração capilar, indicativo de invasão de macrófagos, atraso na mielinização e gliose em modelos animais (127). No entanto, a associação entre anormalidades da substância branca e TDAH em neonatos prematuros submetidos à ventilação mecânica prolongada necessita de mais investigação.

Indredavik et al. (2010) (58), num estudo de 65 adolescentes de MBPN, falhou em encontrar associação entre o uso de ventilação mecânica no período neonatal e

sintomas de TDAH. Entretanto, um estudo realizado por Tsai et al. (2014) (128), com um banco de dados nacional, de tamanho amostral bem maior (728 sujeitos), com seguimento retrospectivo de 10 anos, mostrou que indivíduos de EBPN em ventilação mecânica por mais de 15 dias no período neonatal tiveram 1,95 vezes (IC 95%, 1,02–3,76, p<0,05) mais chance de ter TDAH do que os bebês que usavam ventilador por 2 dias ou menos.

2.4.3.8 Retinopatia da Prematuridade

Leviton et al. (2018) (129) estudaram os antecedentes de triagem positiva para TDAH em crianças de 10 anos de idade, nascidas EP. Pais e professores preencheram a *Child Symptom Inventory-4*, que fornece informações sobre os sintomas do TDAH com base nos critérios do *Diagnostic and Statistical Manual of Mental Disorders fifth edition* (DSM-5). Os pais também informaram se um médico havia feito um diagnóstico de TDAH e se medicação havia sido prescrita. Os seguintes fatores de risco apresentaram achados estatisticamente significativos: idade materna jovem, obesidade materna, tabagismo materno, uso de magnésio para profilaxia de convulsão, infecção placentária pelo *Mycoplasma sp*, idade gestacional baixa, baixo peso ao nascer, ser mãe solteira, sexo masculino, ventilação mecânica depois dos 7 dias de nascimento, recebimento de sedativo, retinopatia da prematuridade, enterocolite necrosante, recebimento de antibióticos e ventriculomegalia na tomografia cerebral. No entanto, o perfil de risco da triagem positiva para o TDAH diferiu entre os diferentes tipos de informantes. Para explicar a variável retinopatia da prematuridade, os autores sugeriram que a exposição a um antecedente comum, como hiperóxia relativa (130), ou a uma vulnerabilidade comum associada a uma idade gestacional especialmente baixa (131) poderia explicar esse achado positivo.

2.4.3.9 Hemorragia Peri-intraventricular

Entre prematuros de MBPN, a hemorragia peri-intraventricular (e presumivelmente o dano cerebral resultante (58)) e crescimento cefálico abaixo do

normal (132) estariam associados a dificuldades atencionais. Em um estudo prospectivo, lesões da substância branca detectadas por ultrassom foram associadas com um risco 2,7 vezes maior de TDAH aos 6 anos de idade (133). Imagens de ressonância magnética também têm demonstrado correlatos estruturais de problemas atencionais. Entre os adolescentes de MBPN, o estreitamento do corpo caloso e volume reduzido de substância branca foram associados a dificuldades atencionais, mas não à hiperatividade (134). *Diffuse Tensor Imaging*, que identifica a interrupção ou desorganização da substância branca, indica que anisotropia fracionada reduzida na cápsula externa e em fascículos médio e superior está associada a escores mais altos de desatenção na *ADHD Rating Scale IV* (135).

2.4.3.10 Leucomalácia Periventricular

Choi et al. (2016) (136) investigou desfechos neurodesenvolvimentais de 100 crianças prematuras com leucomalácia periventricular confirmada por ressonância magnética cerebral e revelou associações significativas entre a gravidade da leucomalácia periventricular e funções cognitivas e sociais adaptativas em crianças prematuras. Das 100 crianças, 11 tiveram problemas de atenção/hiperatividade de acordo com a *Conners Parent Rating Scale* abreviada e 26 tiveram problemas de atenção de acordo com as pontuações da CBCL, mas não foi demonstrada relação entre as frequências de problemas atencionais e os diferentes níveis de gravidade de leucomalácia periventricular.

Especificamente na população com prematuridade/baixo peso ao nascer, uma grande coorte australiana de 189 crianças que nasceram EP/EBPN (137) forneceu fortes evidências de que essa população apresenta maior risco de comprometimento de atenção. O grupo EP/EBPN, em comparação com 173 crianças nascidas a termo/peso normal ao nascer, teve taxas significativamente elevadas de comprometimento da atenção seletiva, sustentada, alternada e dividida, bem como de sintomas de TDAH. Não foram identificados efeitos significativos de gênero ou gradiente de idade gestacional. Entre todos os fatores neonatais analisados neste estudo (idade gestacional, peso ao nascer, sexo, displasia broncopulmonar,

corticosteroides pós-natais, enterocolite necrosante, leucomalácia periventricular cística e hemorragia intraventricular grau 3 ou 4) apenas enterocolite necrosante (t=2,3, p=0,026) e leucomalácia periventricular cística (t=-2,1, p=0,035) foram preditores independentes de atenção seletiva prejudicada aos 8 anos de idade. Como isso não foi encontrado para outros domínios de atenção, os autores concluíram que os fatores neonatais não eram independentes, mas estavam relacionados e tendiam a coexistir, e essa multicolinearidade explicaria em parte por que os preditores selecionados não estavam relacionados de forma independente a outros domínios de atenção além da atenção seletiva. Apesar disso, a variância explicada dos domínios de atenção pelos fatores de risco neonatais em conjunto foi apenas modesta (4 a 11%).

Um estudo que avaliou efeitos de longo prazo da leucomalácia periventricular na espessura cortical e sua relação com anormalidades cognitivas e comportamentais mostrou que um aumento atípico na espessura cortical pode ser responsável por problemas comportamentais em crianças prematuras com leucomalácia periventricular (138). Neste estudo, os escores de problemas atencionais foram maiores na leucomalácia periventricular e correlacionados com os incrementos da espessura cortical nas áreas frontais direitas. Outra pesquisa sugeriu que a localização do infarto hemorrágico periventricular no lobo temporal ou frontal parecia estar relacionada a problemas comportamentais em crianças prematuras (139).

2.4.3.11 Convulsões Neonatais

Convulsões neonatais têm sido associadas a transtornos comportamentais de longo prazo, incluindo o TDAH (140-142). Como essa condição envolve alterações na função do lobo pré-frontal (143, 144), postula-se que os substratos neurológicos subjacentes ao TDAH possam ser permanentemente alterados por convulsões que ocorrem no início da vida. Uma grande coorte populacional de todas as crianças nascidas na Dinamarca de 1990 a 2007, acompanhada até 2012, mostrou uma forte associação entre epilepsia na infância e desenvolvimento subsequente de TDAH, mesmo após o ajuste para fatores de risco socioeconômicos, perinatais e histórico

familiar de epilepsia, convulsões febris ou transtornos psiquiátricos (145). Neste estudo, crianças com epilepsia tiveram uma taxa de incidência ajustada de TDAH de 2,72 (IC 95%, 2,53–2,91) em comparação com crianças sem epilepsia. Pineda et al. (2007) (146) encontraram associação entre convulsões neonatais e TDAH (RC ajustado: 5,6; IC 95%, 1,4–22,5) em uma amostra colombiana de 200 crianças com TDAH entre 6 e 11 anos de idade e 286 controles saudáveis. No entanto, como discutido por Serati et al. (2017) (56) em uma revisão sistemática do papel de complicações obstétricas e neonatais no TDAH na infância, esses dados são muito fracos para tirar conclusões definitivas sobre a associação entre convulsões neonatais e TDAH.

2.4.3.12 Circunferência da Cabeça

O crescimento restrito do cérebro no período fetal pode ser um fator de risco para o desenvolvimento de TDAH. Alguns estudos prévios (147, 148) associam uma circunferência da cabeça menor ao nascimento com uma frequência mais alta de sintomas de TDAH, mas outros não encontraram essa associação (149). Numa população de 893 indivíduos, Heinonen et al. (2011) (148) encontraram que uma menor circunferência da cabeça ao nascimento estava relacionada a mais sintomas de TDAH aos 56 meses de vida. Outro estudo semelhante, de Lahti et al. (2006) (147), encontrou uma associação protetora entre circunferência da cabeça maior ao nascimento e TDAH. Ele também sugeriu que essa medida era um preditor mais forte de sintomas de hiperatividade e desatenção do que o próprio peso ao nascer (147). Já Murray et al. (2015) (107), em um estudo de coorte de 3.749 nascimentos não encontrou associação entre parâmetros de crescimento pré-natal e sintomas de TDAH, somente quando estratificou as análises por sexo. As meninas com circunferência da cabeça menor estavam associadas positivamente aos problemas de atenção na CBCL (107). Ferrer et al. (2018) (150), em uma grande amostra populacional encontrou associações independentes entre os escores z de circunferência da cabeça ao nascimento e sintomas de desatenção pelo *Diagnostic and Statistical Manual of Mental Disorders fourth edition* (DSM-IV) aos 1–1,5 anos e

aos 4 anos, enquanto que os sintomas de impulsividade e hiperatividade não foram associados a nenhuma medida de circunferência da cabeça pré-natal, neonatal ou pós-natal.

Em um estudo de coorte nacional dinamarquês baseado em registros sobre circunferência da cabeça ao nascer e transtornos do desenvolvimento infantil (151), microcefalia foi associada a um risco aumentado de TDAH [Hazard Ratio (HR): 1,22; IC 95%, 1,12–1,32]. A macrocefalia foi associada a um risco ligeiramente reduzido de TDAH (HR: 0,90; IC 95%, 0,82–0,99). A associação entre microcefalia e TDAH foi um pouco mais forte em crianças nascidas prematuras. Essas associações, no entanto, desapareceram quando foram feitas análises nos seus irmãos. Análises em crianças normocefálicas mostraram associação entre menor perímetro cefálico e aumento do risco de TDAH. Uma circunferência da cabeça no limite inferior da normocefalia em comparação com uma circunferência da cabeça no limite superior foi associada a um risco aumentado de TDAH (HR: 1,52; IC 95%, 1,43–1,63), mesmo após comparações com os irmãos. Além disso, também existem estudos que relataram relações entre pequeno volume cerebral e sintomas de TDAH (152-154).

2.4.3.13 Pequeno para a Idade Gestacional

É provável que o crescimento fetal restrito atue na via causal do TDAH devido à diminuição da nutrição no útero, levando ao desenvolvimento cerebral perturbado e, consequentemente, a problemas no neurodesenvolvimento (70). Um estudo de 2015 mostrou que, entre pares de gêmeos monozigóticos, sintomas de TDAH estavam relacionados às diferenças de peso de nascimento entre eles (70).

Em um estudo de Tanis et al. (2012) (155), 28 crianças MP e PIG, nascidas entre 2000 e 2001, foram comparadas com 28 crianças MP, mas Adequadas para Idade Gestacional (AIG), pareadas por idade gestacional, sexo e ano de nascimento. Aos 8,6 anos, as crianças PIG obtiveram pontuações mais baixas na atenção seletiva (p=0,026) e percepção visual (p=0,025). A mediana do QI total das crianças PIG foi de 94 em comparação com 95 nos controles (não significativo). O QI de desempenho foi significativamente menor em crianças PIG (89 vs. 95, p=0,043), enquanto o QI

verbal não foi (95 vs. 95). Além disso, as habilidades motoras totais (p=0,048) e as habilidades motoras finas (p=0,021) foram piores em crianças PIG. Os autores concluíram que as diferenças entre os grupos eram pequenas, sugerindo que o comprometimento do funcionamento de crianças PIG MP é atribuível ao fato de terem nascido MP e não ao fato de serem PIG.

Em um estudo realizado por Sucksdorff et al. (2015) (156), bebês nascidos PIG (menor ou igual a 2 DP) apresentaram risco duas vezes maior de TDAH na análise univariada e, após o ajuste para fatores de confusão, a RC foi de 1,80 (IC 95%, 1,58–2,05). Um risco significativamente aumentado também foi observado nos grupos de peso para a idade gestacional de -2,0 a -1,5 DP e de -1,5 a -1,0 DP, resultando em RCs ajustadas de 1,36 (IC 95%, 1,21–1,52) e 1,14 (IC 95%, 1,04–1,24), respectivamente. Os bebês nascidos grandes para a idade gestacional (GIG, acima de 2 DP) tiveram risco aumentado em 1,21 vezes (IC 95%, 1,05–1,40), de acordo com o modelo ajustado.

No entanto, um grande estudo de coorte (157) encontrou uma associação entre o status PIG e problemas de atenção apenas entre meninas nascidas a termo, e outro estudo não encontrou um risco aumentado de TDAH entre crianças PIG no modelo ajustado (158).

2.4.3.14 Nutrição Parenteral e Recuperação do Peso ao Nascer

Bebês prematuros, especialmente os de MBPN e EBPN, são suscetíveis a falhas de crescimento na vida pós-natal se as demandas nutricionais não forem atendidas. O baixo crescimento pós-natal em prematuros está associado a desfechos adversos no neurodesenvolvimento durante a infância (159). A nutrição parenteral precoce é de suma importância para fornecer proteína e energia apropriadas em bebês de MBPN quando a nutrição enteral não é viável ou está abaixo do ideal. Foi demonstrado que o uso precoce da nutrição parenteral em bebês prematuros previne o catabolismo proteico, induz o balanço positivo de nitrogênio, diminui a perda de peso pós-natal, reduz mortalidade, incidência de displasia broncopulmonar, enterocolite

necrosante, melhora o crescimento pós-natal e possivelmente melhora os desfechos neurodesenvolvimentais (159, 160).

2.4.3.15 Enterocolite Necrosante

Em uma coorte (161) de crianças nascidas entre 1994 e 2000 no Reino Unido, avaliando as consequências a longo prazo do diagnóstico de enterocolite necrosante neonatal confirmada ou suspeita, sintomas de TDAH relatados pelos pais na *Strengths and Difficulties Questionnaire* (SDQ) aos 7 anos foram associados à ocorrência de enterocolite necrosante no período neonatal na análise univariada [18/118 (15%) nos com enterocolite necrosante vs. 462/6316 (7%) no grupo sem enterocolite necrosante; RC: 2,24; IC 95%, 1,34–3,72]. No entanto, como esse risco maior não se confirmou nas análises ajustadas, os autores concluíram que essa associação com TDAH era mediada por outras morbidades neonatais associadas à enterocolite necrosante.

Como já relatado acima, especificamente na população com prematuridade/baixo peso ao nascer, uma grande coorte australiana de 189 crianças que nasceram EP/EBPN (137) forneceu fortes evidências de que essa população apresenta maior risco de comprometimento de atenção. O grupo EP/EBPN, em comparação com 173 crianças nascidas a termo/peso normal ao nascer, teve taxas significativamente elevadas de comprometimento da atenção seletiva, sustentada, alternada e dividida, bem como de sintomas de TDAH. Não foram identificados efeitos significativos de gênero ou gradiente de idade gestacional. Entre todos os fatores neonatais analisados neste estudo (idade gestacional, peso ao nascer, sexo, displasia broncopulmonar, corticosteroides pós-natais, enterocolite necrosante, leucomalácia periventricular cística e hemorragia intraventricular grau 3 ou 4) apenas enterocolite necrosante (t=2,3, p=0,026) e leucomalácia periventricular cística (t=-2,1, p=0,035) foram preditores independentes de atenção seletiva prejudicada aos 8 anos de idade. Como isso não foi encontrado para outros domínios de atenção, os autores concluíram que os fatores neonatais não eram independentes, mas estavam relacionados e tendiam a coexistir, e essa multicolinearidade explicaria em parte por que os preditores selecionados não estavam relacionados de forma independente a outros

domínios de atenção além da atenção seletiva. Apesar disso, a variância explicada dos domínios de atenção pelos fatores de risco neonatais em conjunto foi apenas modesta (4 a 11%).

2.4.3.16 Sepse

Sepse tardia (sepse após 72 horas de vida), é uma complicação relativamente comum do nascimento prematuro, afetando 21% dos recém-nascidos de MBPN (162). Num estudo prospectivo caso-controle (163), 32 crianças MP/MBPN de 6 a 9 anos que tiveram sepse tardia comprovada por hemocultura após o nascimento, quando comparadas a 18 controles pareados por idade gestacional, tiveram pior controle atencional (DP: 0,94; IC 95%, 0,32–1,62, p=0,011) e de memória (DP: 0,61; IC 95%, 0,04–1,17, p=0,033) nas testagens neuropsicológicas. No entanto, nenhuma associação foi encontrada para sintomas de TDAH. A maioria deles também teve problemas motores (68%) e seu QI foi consideravelmente menor do que nos controles (89 vs. 98).

Já em uma coorte regional de 110 crianças nascidas MP na Nova Zelândia (164), infecção neonatal confirmada aumentou o risco para problemas de neurodesenvolvimento aos 9 anos de idade (risco relativo de 1,4 a 3,1, comparado aos não-infectados). Mesmo após o ajuste para sexo, restrição de crescimento intrauterino, idade gestacional ao nascimento, suporte inotrópico e risco social da família, a infecção neonatal permaneceu um preditor independente significativo de TDAH (RC: 3,6; IC 95%, 1,6–8; p=0,001), comprometimento motor grave (RC: 3,3; IC 95%, 1,3–8; p=0,01) e, marginalmente, atraso cognitivo (RC: 2,0; IC 95%, 1–3,9; p=0,05). Eles também descobriram que uma infecção suspeita apresenta menos risco ao desenvolvimento do que uma infecção confirmada. Outro estudo (84) constatou que bebês EP com níveis sanguíneos elevados de proteínas relacionadas à inflamação tinham maior probabilidade de apresentar problemas de comportamento aos 24 meses de idade, sendo déficits de atenção os mais comuns.

2.4.3.17 Tempo de Internação Hospitalar

Uma longa permanência do bebê MP/MBPN no hospital, influenciada principalmente pela idade gestacional ao nascimento e pelas suas condições clínicas (165), pode expô-lo a riscos associados ao ambiente hospitalar. Isso inclui luzes brilhantes, excesso de barulho, infecções hospitalares, exposição a produtos químicos por meio de equipamento médico, interação social restrita entre pais e bebê (166, 167), que são importantes para os desfechos neurocomportamentais a longo prazo nessa população (167). O estresse relacionado à dor neonatal prediz espessura cortical aos 7 anos de idade em crianças nascidas muito prematuras (168) e está relacionado a problemas de neurodesenvolvimento (169, 170). Comparados com bebês menos expostos ao estresse, bebês prematuros com níveis mais altos de exposição ao estresse apresentam alterações na estrutura do cérebro quando atingem a idade equivalente ao bebê nascido a termo (171). A inflamação crônica pode ser uma possível mediadora, uma vez que altos níveis sustentados de citocinas pró-inflamatórias estão associados a problemas de neurodesenvolvimento (172).

2.5 MODELOS DE PREDIÇÃO E CALCULADORAS DE RISCO

Nas últimas décadas, várias áreas da medicina começaram a elaborar modelos preditivos para avaliar como uma combinação de fatores de risco e proteção influencia o risco de desenvolver doenças (173). A partir desses modelos, é possível construir calculadoras de risco, que permitem ao clínico inserir variáveis relevantes e estimar a probabilidade de um determinado resultado ocorrer durante um determinado período. Uma das calculadoras de risco mais conhecida é a Framingham Risk Score (174), que é usada para estratificar o risco de doença cardiovascular após um período de 10 anos. Ela apresenta boa discriminação (área sob a curva, (em inglês, AUC) de 0.763 para homens e 0.793 para mulheres) e calibração, possibilitando assim intervir adequadamente para diminuir o risco.

Apesar de ainda ser limitado, o desenvolvimento desses modelos em psiquiatria tem aumentado nos últimos anos. Uma recente revisão sistemática de

Bernardini et al. (2017) (175) mostrou que é viável desenvolver modelos de predição de risco para transtornos psiquiátricos. Essa revisão encontrou 24 estudos que desenvolveram modelos de predição para transtornos psicóticos, 12 para transtorno depressivo maior, 4 para transtorno de estresse pós-traumático, 2 para transtorno de ansiedade generalizada e 1 para transtorno bipolar. De maneira geral, os autores encontraram bons resultados, principalmente para transtornos psicóticos.

Não temos conhecimento de tentativas anteriores de criar uma calculadora de risco para prever o diagnóstico de TDAH em recém-nascidos MP/MBPN. Um estudo de Scwenke et al. (2018) (176) usou características de gravidez e nascimento para prever o TDAH em uma coorte hospitalar de nascimentos, mas não se concentraram na população MP/MBPN. Neste estudo, apenas o tabagismo e o índice de Apgar 1 minuto após o nascimento foram preditores de TDAH no modelo de regressão logística multivariável. O tabagismo durante a gravidez apresentou uma RC de 2,63 (IC 95%, 1,39–4,97), e um maior índice de Apgar foi associado a um menor risco de TDAH na criança (RC: 0,76; IC 95%, 0,61–0,94). Não foram encontradas associações significativas com o desenvolvimento posterior de TDAH para os escores de Apgar aos 5 e 10 minutos após o trabalho de parto, modo de parto, nível educacional da mãe, número de gravidezes, aleitamento materno, uso de álcool durante a gravidez, idade no momento do trabalho de parto, peso ao nascer, valor do pH da artéria umbilical ou duração da gravidez. No entanto, este estudo teve um seguimento de apenas 15,4% e vários fatores de risco e desfechos potenciais foram coletados retrospectivamente com base em questionários enviados à mãe. Para o TDAH, por exemplo, foi perguntado à mãe apenas se sabia que seu filho tinha um diagnóstico de TDAH e se a criança estava tomando medicação para a doença. Nenhuma calculadora de risco foi desenvolvida neste estudo.

Em outro estudo, Caye et al. (2019) (177) desenvolveram uma calculadora de risco baseada em características da infância para prever TDAH na vida adulta, com desempenho satisfatório (AUC: 0,82 (IC 95%, 0,79–0,83). Esta calculadora de risco incluiu os seguintes preditores: sexo, status socioeconômico, família monoparental, sintomas de TDAH, transtornos disruptivos comórbidos, maus-tratos na infância, depressão materna e QI.

Em suma, a prematuridade e o baixo peso ao nascer são problemas de saúde pública muito significativos, dada a sua prevalência, mortalidade e morbidade, especialmente nos indivíduos MP/MBPN. A ocorrência aumentada de fatores de risco entre os pacientes prematuros ou com muito baixo peso ao nascer para o desenvolvimento de TDAH provavelmente reflete mais um somatório de complicações observadas durante a gestação, durante o parto ou no período neonatal do que um fator de risco independente. Desta forma, o papel de cada um dos fatores de risco para TDAH na população de MP/MBPN necessita ser esclarecido. Até o momento ainda não existem modelos preditivos que avaliem o peso que cada fator pré-natal ou neonatal exerce no risco de desenvolvimento de TDAH, nem calculadoras para quantificar esse risco.

3. REFERÊNCIAS BIBLIOGRÁFICAS

1. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta obstetricia et gynecologica Scandinavica. 1977;56(3):247-53.

2. Tucker J, McGuire W. Epidemiology of preterm birth. Bmj. 2004;329(7467):675-8.

3. Hughes MM, Black RE, Katz J. 2500-g Low Birth Weight Cutoff: History and Implications for Future Research and Policy. Maternal and child health journal. 2017;21(2):283-9.

4. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global health. 2019;7(1):e37-e46.

5. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

6. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. The Lancet Global health. 2019;7(7):e849-e60.

7. Martin, J. A., Hamilton, B. E., Osterman, M. J., Curtin, S. C., & Matthews, T. J. (2015). Births: final data for 2013. National vital statistics reports: from the centers for disease control and prevention, national center for health statistics, national vital statistics system, 64, 1–65.

8. Brasil. Ministério da Saúde. DATASUS. Sistema de Informações sobre Nascidos Vivos – SINASC. Disponível em http://datasus.gov.br. Acesso em dezembro de 2019.

9. Goldenberg RL, Gravett MG, Iams J, Papageorghiou AT, Waller SA, Kramer M, et al. The preterm birth syndrome: issues to consider in creating a classification system. American journal of obstetrics and gynecology. 2012;206(2):113-8.

10. Lawn JE, Kinney M, Lee AC, Chopra M, Donnay F, Paul VK, et al. Reducing intrapartum-related deaths and disability: can the health system deliver? International journal of gynaecology and obstetrics: the official organ of the

International Federation of Gynaecology and Obstetrics. 2009;107 Suppl 1:S123-40, S40-2.

11. Gyamfi-Bannerman C, Fuchs KM, Young OM, Hoffman MK. Nonspontaneous late preterm birth: etiology and outcomes. American journal of obstetrics and gynecology. 2011;205(5):456 e1-6.

12. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta obstetricia et gynecologica Scandinavica. 2008;87(6):590-600.

13. Plunkett J, Muglia LJ. Genetic contributions to preterm birth: implications from epidemiological and genetic association studies. Annals of medicine. 2008;40(3):167-95.

14. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. The New England journal of medicine. 2010;362(6):529-35.

15. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.

16. Althabe F, Moore JL, Gibbons L, Berrueta M, Goudar SS, Chomba E, et al. Adverse maternal and perinatal outcomes in adolescent pregnancies: The Global Network's Maternal Newborn Health Registry study. Reproductive health. 2015;12 Suppl 2:S8.

17. Amegah AK, Quansah R, Jaakkola JJ. Household air pollution from solid fuel use and risk of adverse pregnancy outcomes: a systematic review and meta-analysis of the empirical evidence. PloS one. 2014;9(12):e113920.

18. Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. PloS one. 2017;12(10):e0186287.

19. Pereira PP, Da Mata FA, Figueiredo AC, de Andrade KR, Pereira MG. Maternal Active Smoking During Pregnancy and Low Birth Weight in the Americas: A Systematic Review and Meta-analysis. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2017;19(5):497-505.

20. Petrou S, Henderson J, Bracewell M, Hockley C, Wolke D, Marlow N, et al. Pushing the boundaries of viability: the economic impact of extreme preterm birth. Early human development. 2006;82(2):77-84.

21. Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E. Deaths: Final Data for 2016. National vital statistics reports : from the Centers for Disease Control and

Prevention, National Center for Health Statistics, National Vital Statistics System. 2018;67(5):1-76.

22. UN Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality: Report 2017. New York: United Nations Children's Fund, 2017.

23. Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. Anesthesia and analgesia. 2015;120(6):1337-51.

24. Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. Bmj. 2008;336(7655):1221-3.

25. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. American journal of obstetrics and gynecology. 2007;196(2):147 e1-8.

26. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3):443-56.

27. Eichenwald EC, Stark AR. Management and outcomes of very low birth weight. The New England journal of medicine. 2008;358(16):1700-11.

28. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. Archives of pediatrics & adolescent medicine. 1998;152(5):425-35.

29. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. Jama. 2002;288(6):728-37.

30. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009;124(2):717-28.

31. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR, et al. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Archives of disease in childhood Fetal and neonatal edition. 2005;90(2):F134-40.

32. Serenius F, Kallen K, Blennow M, Ewald U, Fellman V, Holmstrom G, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. Jama. 2013;309(17):1810-20.

33. American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.

34. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. Journal of child psychology and psychiatry, and allied disciplines. 2015;56(3):345-65.

35. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychological medicine. 2006;36(2):159-65.

36. Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. The lancet Psychiatry. 2015;2(8):702-9.

37. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet. 2005;366(9481):237-48.

38. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Archives of general psychiatry. 1993;50(7):565-76.

39. Galera C, Melchior M, Chastang JF, Bouvard MP, Fombonne E. Childhood and adolescent hyperactivity-inattention symptoms and academic achievement 8 years later: the GAZEL Youth study. Psychological medicine. 2009;39(11):1895-906.

40. Peasgood T, Bhardwaj A, Biggs K, Brazier JE, Coghill D, Cooper CL, et al. The impact of ADHD on the health and well-being of ADHD children and their siblings. European child & adolescent psychiatry. 2016;25(11):1217-31.

41. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. The Journal of clinical psychiatry. 2006;67(4):524-40.

42. Chang Z, Lichtenstein P, D'Onofrio BM, Sjolander A, Larsson H. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA psychiatry. 2014;71(3):319-25.

43. Klein RG, Mannuzza S, Olazagasti MA, Roizen E, Hutchison JA, Lashua EC, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Archives of general psychiatry. 2012;69(12):1295-303.

44. Lichtenstein P, Larsson H. Medication for attention deficit-hyperactivity disorder and criminality. The New England journal of medicine. 2013;368(8):776.

45. Hechtman L, Swanson JM, Sibley MH, Stehli A, Owens EB, Mitchell JT, et al. Functional Adult Outcomes 16 Years After Childhood Diagnosis of Attention-Deficit/Hyperactivity Disorder: MTA Results. Journal of the American Academy of Child and Adolescent Psychiatry. 2016;55(11):945-52 e2.

46. Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood - a naturalistic long-term follow-up study. Addictive behaviors. 2014;39(1):325-8.

47. Furczyk K, Thome J. Adult ADHD and suicide. Attention deficit and hyperactivity disorders. 2014;6(3):153-8.

48. Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet. 2015;385(9983):2190-6.

49. Munoz-Silva A, Lago-Urbano R, Sanchez-Garcia M, Carmona-Marquez J. Child/Adolescent's ADHD and Parenting Stress: The Mediating Role of Family Impact and Conduct Problems. Frontiers in psychology. 2017;8:2252.

50. Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. Journal of the American Academy of Child and Adolescent Psychiatry. 2012;51(10):990-1002 e2.

51. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. Current psychiatry reports. 2017;19(1):1.

52. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta paediatrica. 2007;96(9):1269-74.

53. Halperin JM, Bedard AC, Curchack-Lichtin JT. Preventive interventions for ADHD: a neurodevelopmental perspective. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2012;9(3):531-41.

54. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. Journal of developmental and behavioral pediatrics : JDBP. 2009;30(2):122-30.

55. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in

the EPICure study. Journal of the American Academy of Child and Adolescent Psychiatry. 2010;49(5):453-63 e1.

56. Serati M, Barkin JL, Orsenigo G, Altamura AC, Buoli M. Research Review: The role of obstetric and neonatal complications in childhood attention deficit and hyperactivity disorder - a systematic review. Journal of child psychology and psychiatry, and allied disciplines. 2017;58(12):1290-300.

57. Momany AM, Kamradt JM, Nikolas MA. A Meta-Analysis of the Association Between Birth Weight and Attention Deficit Hyperactivity Disorder. Journal of abnormal child psychology. 2018;46(7):1409-26.

58. Indredavik MS, Vik T, Evensen KA, Skranes J, Taraldsen G, Brubakk AM. Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. Journal of developmental and behavioral pediatrics : JDBP. 2010;31(4):286-94.

59. Johnson S, Wolke D. Behavioural outcomes and psychopathology during adolescence. Early human development. 2013;89(4):199-207.

60. Johnson S, Kochhar P, Hennessy E, Marlow N, Wolke D, Hollis C. Antecedents of Attention-Deficit/Hyperactivity Disorder Symptoms in Children Born Extremely Preterm. Journal of developmental and behavioral pediatrics : JDBP. 2016;37(4):285-97.

61. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. Archives of disease in childhood Fetal and neonatal edition. 2004;89(5):F445-50.

62. Johnson S. Cognitive and behavioural outcomes following very preterm birth. Seminars in fetal & neonatal medicine. 2007;12(5):363-73.

63. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. Attention problems in very preterm children from childhood to adulthood: the Bavarian Longitudinal Study. Journal of child psychology and psychiatry, and allied disciplines. 2016;57(2):132-40.

64. Anderson PJ, Doyle LW, Victorian Infant Collaborative Study G. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. Pediatrics. 2004;114(1):50-7.

65. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240-50.

66. Elgen I, Sommerfelt K, Markestad T. Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. Archives of disease in childhood Fetal and neonatal edition. 2002;87(2):F128-32.

67. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Molecular psychiatry. 2019;24(4):562-75.

68. Lunde A, Melve KK, Gjessing HK, Skjaerven R, Irgens LM. Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. American journal of epidemiology. 2007;165(7):734-41.

69. Boivin A, Luo ZC, Audibert F, Masse B, Lefebvre F, Tessier R, et al. Risk for preterm and very preterm delivery in women who were born preterm. Obstetrics and gynecology. 2015;125(5):1177-84.

70. Pettersson E, Sjolander A, Almqvist C, Anckarsater H, D'Onofrio BM, Lichtenstein P, et al. Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. Journal of child psychology and psychiatry, and allied disciplines. 2015;56(4):453-9.

71. Lim KX, Liu CY, Schoeler T, Cecil CAM, Barker ED, Viding E, et al. The role of birth weight on the causal pathway to child and adolescent ADHD symptomatology: a population-based twin differences longitudinal design. Journal of child psychology and psychiatry, and allied disciplines. 2018;59(10):1036-43.

72. Groen-Blokhuis MM, Middeldorp CM, van Beijsterveldt CE, Boomsma DI. Evidence for a causal association of low birth weight and attention problems. Journal of the American Academy of Child and Adolescent Psychiatry. 2011;50(12):1247-54 e2.

73. Leppert B, Havdahl A, Riglin L, Jones HJ, Zheng J, Davey Smith G, et al. Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. JAMA psychiatry. 2019.

74. Barker DJ. Maternal nutrition, fetal nutrition, and disease in later life. Nutrition. 1997;13(9):807-13.

75. Barker DJ. The origins of the developmental origins theory. Journal of internal medicine. 2007;261(5):412-7.

76. Mandy M, Nyirenda M. Developmental Origins of Health and Disease: the relevance to developing nations. International health. 2018;10(2):66-70.

77. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Seminars in reproductive medicine. 2009;27(5):358-68.

78. Gillman MW. Developmental origins of health and disease. The New England journal of medicine. 2005;353(17):1848-50.

79. Smith TF, Schmidt-Kastner R, McGeary JE, Kaczorowski JA, Knopik VS. Pre- and Perinatal Ischemia-Hypoxia, the Ischemia-Hypoxia Response Pathway, and ADHD Risk. Behavior genetics. 2016;46(3):467-77.

80. Singhal A. Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth. Annals of nutrition & metabolism. 2017;70(3):236-40.

81. Dunn GA, Nigg JT, Sullivan EL. Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. Pharmacology, biochemistry, and behavior. 2019;182:22-34.

82. Bhattacharya A, Derecki NC, Lovenberg TW, Drevets WC. Role of neuro-immunological factors in the pathophysiology of mood disorders. Psychopharmacology. 2016;233(9):1623-36.

83. Oades RD, Dauvermann MR, Schimmelmann BG, Schwarz MJ, Myint AM. Attention-deficit hyperactivity disorder (ADHD) and glial integrity: S100B, cytokines and kynurenine metabolism--effects of medication. Behavioral and brain functions : BBF. 2010;6:29.

84. O'Shea TM, Joseph RM, Kuban KC, Allred EN, Ware J, Coster T, et al. Elevated blood levels of inflammation-related proteins are associated with an attention problem at age 24 mo in extremely preterm infants. Pediatric research. 2014;75(6):781-7.

85. Niu Z, Xie C, Wen X, Tian F, Yuan S, Jia D, et al. Potential pathways by which maternal second-hand smoke exposure during pregnancy causes full-term low birth weight. Scientific reports. 2016;6:24987.

86. Marsh R, Gerber AJ, Peterson BS. Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2008;47(11):1233-51.

87. Lindstrom K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. Pediatrics. 2011;127(5):858-65.

88. Scott MN, Taylor HG, Fristad MA, Klein N, Espy KA, Minich N, et al. Behavior disorders in extremely preterm/extremely low birth weight children in

kindergarten. Journal of developmental and behavioral pediatrics : JDBP. 2012;33(3):202-13.

89. Adler N, Bush NR, Pantell MS. Rigor, vigor, and the study of health disparities. Proceedings of the National Academy of Sciences of the United States of America. 2012;109 Suppl 2:17154-9.

90. Gray SC, Edwards SE, Schultz BD, Miranda ML. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. Environmental health : a global access science source. 2014;13(1):4.

91. Silal SP, Penn-Kekana L, Harris B, Birch S, McIntyre D. Exploring inequalities in access to and use of maternal health services in South Africa. BMC health services research. 2012;12:120.

92. Larsson H, Sariaslan A, Langstrom N, D'Onofrio B, Lichtenstein P. Family income in early childhood and subsequent attention deficit/hyperactivity disorder: a quasi-experimental study. Journal of child psychology and psychiatry, and allied disciplines. 2014;55(5):428-35.

93. Xiang AH, Wang X, Martinez MP, Getahun D, Page KA, Buchanan TA, et al. Maternal Gestational Diabetes Mellitus, Type 1 Diabetes, and Type 2 Diabetes During Pregnancy and Risk of ADHD in Offspring. Diabetes care. 2018;41(12):2502-8.

94. Zeng Y, Tang Y, Yue Y, Li W, Qiu X, Hu P, et al. Cumulative evidence for association of parental diabetes mellitus and attention-deficit/hyperactivity disorder. Neuroscience and biobehavioral reviews. 2019.

95. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PloS one. 2014;9(12):e113715.

96. Olson-Chen C, Seligman NS. Hypertensive Emergencies in Pregnancy. Critical care clinics. 2016;32(1):29-41.

97. Getahun D, Rhoads GG, Demissie K, Lu SE, Quinn VP, Fassett MJ, et al. In utero exposure to ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. Pediatrics. 2013;131(1):e53-61.

98. Maher GM, O'Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, et al. Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. JAMA psychiatry. 2018;75(8):809-19.

99. Spencer RN, Carr DJ, David AL. Treatment of poor placentation and the prevention of associated adverse outcomes--what does the future hold? Prenatal diagnosis. 2014;34(7):677-84.

100. Nomura Y, John RM, Janssen AB, Davey C, Finik J, Buthmann J, et al. Neurodevelopmental consequences in offspring of mothers with preeclampsia during pregnancy: underlying biological mechanism via imprinting genes. Archives of gynecology and obstetrics. 2017;295(6):1319-29.

101. Pinheiro TV, Brunetto S, Ramos JG, Bernardi JR, Goldani MZ. Hypertensive disorders during pregnancy and health outcomes in the offspring: a systematic review. Journal of developmental origins of health and disease. 2016;7(4):391-407.

102. Bohm S, Curran EA, Kenny LC, O'Keeffe GW, Murray D, Khashan AS. The Effect of Hypertensive Disorders of Pregnancy on the Risk of ADHD in the Offspring. Journal of attention disorders. 2019;23(7):692-701.

103. Mann JR, McDermott S. Are maternal genitourinary infection and pre-eclampsia associated with ADHD in school-aged children? Journal of attention disorders. 2011;15(8):667-73.

104. Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: preterm birth and effects on development. Journal of pregnancy. 2013;2013:412831.

105. Raghavan R, Helfrich BB, Cerda SR, Ji Y, Burd I, Wang G, et al. Preterm birth subtypes, placental pathology findings, and risk of neurodevelopmental disabilities during childhood. Placenta. 2019;83:17-25.

106. Ask H, Gustavson K, Ystrom E, Havdahl KA, Tesli M, Askeland RB, et al. Association of Gestational Age at Birth With Symptoms of Attention-Deficit/Hyperactivity Disorder in Children. JAMA pediatrics. 2018;172(8):749-56.

107. Murray E, Matijasevich A, Santos IS, Barros AJ, Anselmi L, Barros FC, et al. Sex differences in the association between foetal growth and child attention at age four: specific vulnerability of girls. Journal of child psychology and psychiatry, and allied disciplines. 2015;56(12):1380-8.

108. Momany AM, Kamradt JM, Ullsperger JM, Elmore AL, Nigg JT, Nikolas MA. Sex moderates the impact of birth weight on child externalizing psychopathology. Journal of abnormal psychology. 2017;126(2):244-56.

109. Martel MM. Sexual selection and sex differences in the prevalence of childhood externalizing and adolescent internalizing disorders. Psychological bulletin. 2013;139(6):1221-59.

110. Halmoy A, Klungsoyr K, Skjaerven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. Biological psychiatry. 2012;71(5):474-81.

111. Zhu T, Gan J, Huang J, Li Y, Qu Y, Mu D. Association Between Perinatal Hypoxic-Ischemic Conditions and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis. Journal of child neurology. 2016;31(10):1235-44.

112. Stenninger E, Flink R, Eriksson B, Sahlen C. Long-term neurological dysfunction and neonatal hypoglycaemia after diabetic pregnancy. Archives of disease in childhood Fetal and neonatal edition. 1998;79(3):F174-9.

113. Kuperman S, Johnson B, Arndt S, Lindgren S, Wolraich M. Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD. Journal of the American Academy of Child and Adolescent Psychiatry. 1996;35(8):1009-17.

114. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. The Journal of pediatrics. 2001;138(1):92-100.

115. Logan JW, Dammann O, Allred EN, Dammann C, Beam K, Joseph RM, et al. Early postnatal illness severity scores predict neurodevelopmental impairments at 10 years of age in children born extremely preterm. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(5):606-14.

116. Farel AM, Hooper SR, Teplin SW, Henry MM, Kraybill EN. Very-low-birthweight infants at seven years: an assessment of the health and neurodevelopmental risk conveyed by chronic lung disease. Journal of learning disabilities. 1998;31(2):118-26.

117. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. Seminars in perinatology. 2006;30(4):227-32.

118. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, et al. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003;112(5):e359.

119. Gray PH, O'Callaghan MJ, Poulsen L. Behaviour and quality of life at school age of children who had bronchopulmonary dysplasia. Early human development. 2008;84(1):1-8.

120. Cowan F, Thoresen M. The effects of intermittent positive pressure ventilation on cerebral arterial and venous blood velocities in the newborn infant. Acta paediatrica Scandinavica. 1987;76(2):239-47.

121. Limperopoulos C, Gauvreau KK, O'Leary H, Moore M, Bassan H, Eichenwald EC, et al. Cerebral hemodynamic changes during intensive care of preterm infants. Pediatrics. 2008;122(5):e1006-13.

122. Shah AR, Kurth CD, Gwiazdowski SG, Chance B, Delivoria-Papadopoulos M. Fluctuations in cerebral oxygenation and blood volume during endotracheal suctioning in premature infants. The Journal of pediatrics. 1992;120(5):769-74.

123. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. Pediatric research. 2001;50(6):712-9.

124. Dammann O, O'Shea TM. Cytokines and perinatal brain damage. Clinics in perinatology. 2008;35(4):643-63, v.

125. Alexandrou G, Martensson G, Skiold B, Blennow M, Aden U, Vollmer B. White matter microstructure is influenced by extremely preterm birth and neonatal respiratory factors. Acta paediatrica. 2014;103(1):48-56.

126. Pogribna U, Yu X, Burson K, Zhou Y, Lasky RE, Narayana PA, et al. Perinatal clinical antecedents of white matter microstructural abnormalities on diffusion tensor imaging in extremely preterm infants. PloS one. 2013;8(8):e72974.

127. Loeliger M, Inder T, Cain S, Ramesh RC, Camm E, Thomson MA, et al. Cerebral outcomes in a preterm baboon model of early versus delayed nasal continuous positive airway pressure. Pediatrics. 2006;118(4):1640-53.

128. Tsai WH, Hwang YS, Hung TY, Weng SF, Lin SJ, Chang WT. Association between mechanical ventilation and neurodevelopmental disorders in a nationwide cohort of extremely low birth weight infants. Research in developmental disabilities. 2014;35(7):1544-50.

129. Leviton A, Hooper SR, Hunter SJ, Scott MN, Allred EN, Joseph RM, et al. Antecedents of Screening Positive for Attention Deficit Hyperactivity Disorder in Ten-Year-Old Children Born Extremely Preterm. Pediatric neurology. 2018;81:25-30.

130. Reich B, Hoeber D, Bendix I, Felderhoff-Mueser U. Hyperoxia and the Immature Brain. Developmental neuroscience. 2016;38(5):311-30.

131. Hadi AM, Hamdy IS. Correlation between risk factors during the neonatal period and appearance of retinopathy of prematurity in preterm infants in neonatal intensive care units in Alexandria, Egypt. Clinical ophthalmology. 2013;7:831-7.

132. Peterson J, Taylor HG, Minich N, Klein N, Hack M. Subnormal head circumference in very low birth weight children: neonatal correlates and school-age consequences. Early human development. 2006;82(5):325-34.

133. Whitaker AH, Van Rossem R, Feldman JF, Schonfeld IS, Pinto-Martin JA, Tore C, et al. Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. Archives of general psychiatry. 1997;54(9):847-56.

134. Indredavik MS, Skranes JS, Vik T, Heyerdahl S, Romundstad P, Myhr GE, et al. Low-birth-weight adolescents: psychiatric symptoms and cerebral MRI abnormalities. Pediatric neurology. 2005;33(4):259-66.

135. Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KA, Martinussen M, et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain : a journal of neurology. 2007;130(Pt 3):654-66.

136. Choi JY, Rha DW, Park ES. The Effects of the Severity of Periventricular Leukomalacia on the Neuropsychological Outcomes of Preterm Children. Journal of child neurology. 2016;31(5):603-12.

137. Anderson PJ, De Luca CR, Hutchinson E, Spencer-Smith MM, Roberts G, Doyle LW, et al. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. Developmental neuropsychology. 2011;36(1):57-73.

138. Zubiaurre-Elorza L, Soria-Pastor S, Junque C, Sala-Llonch R, Segarra D, Bargallo N, et al. Cortical thickness and behavior abnormalities in children born preterm. PloS one. 2012;7(7):e42148.

139. Soltirovska Salamon A, Groenendaal F, van Haastert IC, Rademaker KJ, Benders MJ, Koopman C, et al. Neuroimaging and neurodevelopmental outcome of preterm infants with a periventricular haemorrhagic infarction located in the temporal or frontal lobe. Developmental medicine and child neurology. 2014;56(6):547-55.

140. Kaufmann R, Goldberg-Stern H, Shuper A. Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. Journal of child neurology. 2009;24(6):727-33.

141. Dunn DW. Neuropsychiatric aspects of epilepsy in children. Epilepsy & behavior : E&B. 2003;4(2):101-6.

142. Pineda DA, Puerta IC, Merchan V, Arango CP, Galvis AY, Velasquez B, et al. [Perinatal factors associated with attention deficit/hyperactivity diagnosis in Colombian Paisa children]. Revista de neurologia. 2003;36(7):609-13.

143. Sheridan MA, Hinshaw S, D'Esposito M. Efficiency of the prefrontal cortex during working memory in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2007;46(10):1357-66.

144. Kleen JK, Sesque A, Wu EX, Miller FA, Hernan AE, Holmes GL, et al. Early-life seizures produce lasting alterations in the structure and function of the prefrontal cortex. Epilepsy & behavior : E&B. 2011;22(2):214-9.

145. Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalsgaard S. Childhood Epilepsy, Febrile Seizures, and Subsequent Risk of ADHD. Pediatrics. 2016;138(2).

146. Pineda DA, Palacio LG, Puerta IC, Merchan V, Arango CP, Galvis AY, et al. Environmental influences that affect attention deficit/hyperactivity disorder: study of a genetic isolate. European child & adolescent psychiatry. 2007;16(5):337-46.

147. Lahti J, Raikkonen K, Kajantie E, Heinonen K, Pesonen AK, Jarvenpaa AL, et al. Small body size at birth and behavioural symptoms of ADHD in children aged five to six years. Journal of child psychology and psychiatry, and allied disciplines. 2006;47(11):1167-74.

148. Heinonen K, Raikkonen K, Pesonen AK, Andersson S, Kajantie E, Eriksson JG, et al. Trajectories of growth and symptoms of attention-deficit/hyperactivity disorder in children: a longitudinal study. BMC pediatrics. 2011;11:84.

149. Stathis SL, O'Callaghan M, Harvey J, Rogers Y. Head circumference in ELBW babies is associated with learning difficulties and cognition but not ADHD in the school-aged child. Developmental medicine and child neurology. 1999;41(6):375-80.

150. Ferrer M, Garcia-Esteban R, Iniguez C, Costa O, Fernandez-Somoano A, Rodriguez-Delhi C, et al. Head circumference and child ADHD symptoms and cognitive functioning: results from a large population-based cohort study. European child & adolescent psychiatry. 2019;28(3):377-88.

151. Aagaard K, Bach CC, Henriksen TB, Larsen RT, Matthiesen NB. Head circumference at birth and childhood developmental disorders in a nationwide cohort in Denmark. Paediatric and perinatal epidemiology. 2018;32(5):458-66.

152. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. Jama. 2002;288(14):1740-8.

153. Kivilevitch Z, Gabis LV, Katorza E, Achiron R. Fetal cerebral ventricular atria width of 8-10mm: A possible prenatal risk factor for adolescent treated Attention Deficit Hyperactivity Disorder (ADHD). Research in developmental disabilities. 2016;49-50:76-85.

154. O'Dwyer L, Tanner C, van Dongen EV, Greven CU, Bralten J, Zwiers MP, et al. Brain volumetric correlates of autism spectrum disorder symptoms in attention deficit/hyperactivity disorder. PloS one. 2014;9(6):e101130.

155. Tanis JC, van der Ree MH, Roze E, Huis in 't Veld AE, van den Berg PP, Van Braeckel KN, et al. Functional outcome of very preterm-born and small-for-gestational-age children at school age. Pediatric research. 2012;72(6):641-8.

156. Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, et al. Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/ Hyperactivity Disorder. Pediatrics. 2015;136(3):e599-608.

157. O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. Pediatrics. 2003;112(2):301-7.

158. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014;133(1):e14-22.

159. Ehrenkranz RA, Das A, Wrage LA, Poindexter BB, Higgins RD, Stoll BJ, et al. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatric research. 2011;69(6):522-9.

160. Patel P, Bhatia J. Total parenteral nutrition for the very low birth weight infant. Seminars in fetal & neonatal medicine. 2017;22(1):2-7.

161. Pike K, Brocklehurst P, Jones D, Kenyon S, Salt A, Taylor D, et al. Outcomes at 7 years for babies who developed neonatal necrotising enterocolitis: the ORACLE Children Study. Archives of disease in childhood Fetal and neonatal edition. 2012;97(5):F318-22.

162. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285-91.

163. van der Ree M, Tanis JC, Van Braeckel KN, Bos AF, Roze E. Functional impairments at school age of preterm born children with late-onset sepsis. Early human development. 2011;87(12):821-6.

164. Rand KM, Austin NC, Inder TE, Bora S, Woodward LJ. Neonatal Infection and Later Neurodevelopmental Risk in the Very Preterm Infant. The Journal of pediatrics. 2016;170:97-104.

165. Seaton SE, Barker L, Jenkins D, Draper ES, Abrams KR, Manktelow BN. What factors predict length of stay in a neonatal unit: a systematic review. BMJ open. 2016;6(10):e010466.

166. Merritt TA, Pillers D, Prows SL. Early NICU discharge of very low birth weight infants: a critical review and analysis. Seminars in neonatology : SN. 2003;8(2):95-115.

167. Santos J, Pearce SE, Stroustrup A. Impact of hospital-based environmental exposures on neurodevelopmental outcomes of preterm infants. Current opinion in pediatrics. 2015;27(2):254-60.

168. Ranger M, Chau CM, Garg A, Woodward TS, Beg MF, Bjornson B, et al. Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. PloS one. 2013;8(10):e76702.

169. Valeri BO, Holsti L, Linhares MB. Neonatal pain and developmental outcomes in children born preterm: a systematic review. The Clinical journal of pain. 2015;31(4):355-62.

170. Grunau RE, Whitfield MF, Petrie-Thomas J, Synnes AR, Cepeda IL, Keidar A, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain. 2009;143(1-2):138-46.

171. Gorzilio DM, Garrido E, Gaspardo CM, Martinez FE, Linhares MB. Neurobehavioral development prior to term-age of preterm infants and acute stressful events during neonatal hospitalization. Early human development. 2015;91(12):769-75.

172. Leviton A, Allred EN, Fichorova RN, Kuban KC, Michael O'Shea T, Dammann O, et al. Systemic inflammation on postnatal days 21 and 28 and indicators of brain dysfunction 2 years later among children born before the 28th week of gestation. Early human development. 2016;93:25-32.

173. Tripepi G, Heinze G, Jager KJ, Stel VS, Dekker FW, Zoccali C. Risk prediction models. Nephrology, dialysis, transplantation : official publication of the

European Dialysis and Transplant Association - European Renal Association. 2013;28(8):1975-80.

174. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.

175. Bernardini F, Attademo L, Cleary SD, Luther C, Shim RS, Quartesan R, et al. Risk Prediction Models in Psychiatry: Toward a New Frontier for the Prevention of Mental Illnesses. The Journal of clinical psychiatry. 2017;78(5):572-83.

176. Schwenke E, Fasching PA, Faschingbauer F, Pretscher J, Kehl S, Peretz R, et al. Predicting attention deficit hyperactivity disorder using pregnancy and birth characteristics. Archives of gynecology and obstetrics. 2018;298(5):889-95.

177. Caye A, Agnew-Blais J, Arseneault L, Goncalves H, Kieling C, Langley K, et al. A risk calculator to predict adult attention-deficit/hyperactivity disorder: generation and external validation in three birth cohorts and one clinical sample. Epidemiology and psychiatric sciences. 2019:1-9.

4. JUSTIFICATIVAS

a) As taxas de prematuridade/baixo peso ao nascer têm se mantido altas em todo mundo. Além disso, o progresso alcançado em neonatologia tem permitido que recém-nascidos MP/MBPN tenham cada vez mais chances de sobreviver, mantendo as prevalências desta população em alta nas últimas décadas.

b) A população de recém-nascidos MP/MBPN parece ter chances maiores de desenvolver problemas atencionais quando comparada a recém-nascidos a termo, entretanto ainda não há meta-análise desenhada especificamente para avaliar o diagnóstico categórico bem estabelecido de TDAH nesta população.

c) Vários fatores de risco associados à prematuridade/baixo peso ao nascer têm sido implicados no desenvolvimento de TDAH, entretanto a maioria destes foram avaliados individualmente. Ainda não há estudo que quantifique o possível peso que cada fator de risco pré-natal ou neonatal exerce no desenvolvimento futuro de TDAH em recém-nascidos MP/MBPN.

d) A prevalência de TDAH é a mais alta entre os transtornos psiquiátricos externalizantes da infância e adolescência, causando vários prejuízos ao indivíduo, à família e à sociedade.

e) Não há até o momento instrumentos disponíveis para predizer o risco individualizado que recém-nascidos MP/MBPN têm de desenvolver TDAH.

f) Uma melhor compreensão do papel destes fatores de risco pode levar a estratégias de prevenção e intervenção precoce.

5. OBJETIVOS

5.1 OBJETIVO GERAL

O objetivo geral desta tese de doutorado é de estabelecer o risco que crianças MP/MBPN têm de desenvolver o diagnóstico de TDAH e investigar a influência dos fatores de risco associados à prematuridade/baixo peso ao nascer para o desenvolvimento de TDAH. Por fim, produzir um instrumento para predizer o risco individualizado que recém-nascidos MP/MBPN têm de desenvolver TDAH.

5.2 OBJETIVOS ESPECÍFICOS

Artigo 1: Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis

Objetivo Primário:

a) Verificar o risco de indivíduos que nasceram MP/MBPN receberem um diagnóstico categórico de TDAH obtido por instrumentos diagnósticos validados.

Objetivos Secundários:

a) Examinar nessa população o diagnóstico de TDAH de acordo com escalas de classificação dimensional validadas.
b) Descrever as características pré-natais e neonatais mais frequentemente encontradas em indivíduos MP/MBPN que podem estar associados à ocorrência de TDAH.

Artigo 2: Predicting Attention-Deficit/Hyperactivity Disorder in Very Preterm/Very Low Birth Weight Newborns

a) Desenvolver um modelo preditivo multivariável e criar uma calculadora de risco individualizada on-line para ajudar os médicos a identificar, entre os recém-nascidos MP/MBPN, aqueles com maior probabilidade de ter TDAH no futuro usando preditores que são usualmente disponíveis ao nascimento.

6. CONSIDERAÇÕES ÉTICAS

Este projeto foi financiado pelo Programa de Transtornos de Déficit de Atenção/Hiperatividade do HCPA e pelo Fundo de Incentivo à Pesquisa e Eventos do mesmo hospital.

O projeto desta pesquisa foi submetido e aprovado pelo Grupo de Pesquisa e Pós-Graduação e pelo Comitê de Ética em Pesquisa do HCPA (número 15-0384) e foi registrado na Plataforma Brasil (número CAAE: 46376115.1.0000.5327). Não houve prejuízo à assistência ao paciente em momento algum. O Termo de Consentimento Livre e Esclarecido assinado pelos participantes pode ser encontrado no ANEXO 9.3.

7. ARTIGOS

7.1 ARTIGO 1

Título: Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis

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Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis

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Abbreviations:

ADHD: Attention-Deficit/Hyperactivity Disorder
CBCL: Child Behavior Checklist
CI: Confidence Interval
DSM: Diagnostic and Statistical Manual of Mental Disorders
ELBW: Extremely Low Birth Weight
EP: Extremely Preterm
H/I: Hyperactivity/Impulsivity
ICD: International Classification of Diseases
LBW: Low Birth Weight
NBW: Normal Birth Weight
NOS: Newcastle-Ottawa Scale
OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SDQ: Strengths and Difficulties Questionnaire
SMD: Standard Mean Difference
VLBW: Very Low Birth Weight
VP: Very Preterm
WHO: World Health Organization

Table of Contents Summary: This meta-analytic study documents that Very Preterm/Very Low Birth Weight have a higher risk of later Attention-Deficit/Hyperactivity Disorder defined both categorically and dimensionally.

Contributor's Statement Page:

Adelar Pedro Franz conceptualized and designed the study, helped in data collection and drafted the initial manuscript.

Gul Unsel Bolat, Hilmi Bolat, Rita C Silveira and Renato Soibelmann Procianoy Alicia Matijasevich, and Iná Silva Santos helped in data collection and critically reviewed the manuscript.

Luis Augusto Rohde conceptualized and designed the study, helped in data collection and critically reviewed the manuscript.

Carlos Renato Moreira-Maia conceptualized and designed the study, helped in data collection, carried out the analyses and reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Context: Although Very and Extremely Preterm (VP/EP) and Very and Extremely Low Birth Weight (VLBW/ELBW) newborns seem to have a higher risk of later Attention-Deficit/Hyperactivity Disorder (ADHD), the magnitude of the risk is not well-defined.

Objective: To systematically review and meta-analyze the risk of VP/VLBW and EP/ELBW individuals to develop ADHD categorical diagnosis/dimensional symptomatology compared to controls with normal weight and/or birth age.

Data Sources: PsycINFO, MEDLINE, EMBASE, and Cochrane databases.

Study Selection: Cross-sectional, prospective or retrospective studies with no time or language restriction.

Data Extraction: Independent reviewers screened and extracted data using predefined standard procedures.

Results: Twelve studies (n=1,787) relying on categorical diagnosis showed that both VP/VLBW and EP/ELBW subjects have a higher ADHD risk (OR: 3.04 higher than controls; 95% CI, 2.19–4.21). Subgroup analyses demonstrated that the more extreme the cases, the higher the ORs (VP/VLBW, OR: 2.25; 95% CI, 1.56–3.26; EP/ELBW, OR: 4.05; 95% CI, 2.38–6.87). Twenty-nine studies (n=3,504) contributed data on ADHD symptomatology and found significant associations with Inattention (SMD: 1.31; 95% CI, 0.66–1.96), Hyperactivity/Impulsivity (SMD: 0.74; 95% CI, 0.35–1.13), and combined symptoms (SMD: 0.55; 95% CI, 0.42–0.68) when compared to controls.

Limitations: Heterogeneity was significantly high for all analyses involving the three ADHD dimensions.

Conclusions: Our results provide evidence that VP/VLBW subjects have an increased risk of ADHD diagnosis and symptomatology compared to controls and these findings are even stronger in the EP/ELBW group. Future research should address which prematurity/low birth weight-related risk factors lead to ADHD.

INTRODUCTION

Prematurity is an important public health issue due to its high prevalence rates and related morbidity and mortality (1). In 2010, the worldwide prevalence of preterm births was estimated at 11.1% (14.9 million), and a significant amount of these were born Very Preterm (10.4%, 1.6 million) and Extremely Preterm (5.2%, 0.78 million) (2).

Preterm or low birth weight children seem to have more cognitive and psychiatric disorders, as well as an increased risk of Attention-Deficit/Hyperactivity Disorder (ADHD) (3). ADHD is a neurodevelopmental disorder characterized by a non-episodic pattern of inattentive and/or hyperactive/impulsive symptoms, occurring more frequently than expected for the patient's age (4). The worldwide ADHD prevalence is estimated between 3.4 (5) and 5.3% (6) in children and adolescents, and the disorder can persist over time, with an adult prevalence rate of about 2.5% (7). Compared to those with typical development, children and adolescents affected by ADHD frequently present lower educational achievement and self-esteem and higher levels of social impairment, antisocial behavior, and substance abuse, as well as greater involvement in criminal activities and traffic accidents (8, 9).

Some studies suggest a gradient correlation, where the higher the level of prematurity/low birth weight, the higher the ADHD prevalence (10) or risk (11, 12). Thus, Very Preterm (VP)/Very Low Birth Weight (VLBW) and Extremely Preterm (EP)/Extremely Low Birth Weight (ELBW) individuals represent the highest risk groups for ADHD. There is also evidence from a longitudinal prospective cohort study (13) that ADHD diagnosis is more stable in these groups from childhood through adulthood than in term-born individuals.

Despite the data suggesting that VP/VLBW and/or EP/ELBW is clinically relevant to ADHD, no meta-analysis specifically designed to address the risk of VP/VLBW to develop ADHD has been published. Moreover, the very few meta-analyses evaluating associations between more general neurodevelopmental disorders and prematurity/low birth weight present significant shortcomings. A previous meta-analysis (14) of the cognitive and behavioral outcomes of preterm-born school-aged children limited the search to case-control studies and excluded articles

evaluating primarily Low Birth Weight (LBW) children. In addition, the small number of included studies (7 samples from 6 studies) makes its results less robust. This study showed that children born preterm had a 2.64-fold increased risk for ADHD and frequently manifested externalizing symptoms by the time they reached school age. In another meta-analysis (15), VP/VLBW children's academic achievement, behavioral and executive functioning were evaluated, but its literature search was limited to a 10-year span, which could exclude relevant studies. The authors noted that the small number of studies limited the power of some correlational analyses, and they also detected potential publication bias in studies on teacher ratings of behavioral problems.

Although a definitive ADHD etiology has not yet been elucidated, a multifactorial interplay of genes and non-inherited factors are implicated in its causal pathway (16). Several pre-/perinatal factors and preterm morbidities (e.g., necrotizing enterocolitis, periventricular hemorrhage, leukomalacia, bronchopulmonary dysplasia, neonatal chronic lung disease, low Apgar score, white matter injury, slow head growth, etc. (17)) may play a significant role in the etiology of ADHD in premature individuals.

We conducted a systematic review and meta-analysis on the effects of VP/VLBW on ADHD diagnosis and dimensional symptoms. The primary aim of our study was to verify the risk of VP/VLBW and EP/ELBW subjects to be diagnosed with ADHD obtained by validated diagnostic instruments. Our second aim was to examine ADHD diagnosis according to validated dimensional rating scales. Additionally, we sought to describe the most frequent perinatal characteristics, such as clinical/neurological comorbidities found in VP/VLBW subjects that might be associated with the occurrence of ADHD. We hypothesized that there would be a strong and clinically relevant risk of VP/VLBW children, adolescents, and adults to develop categorically- and dimensionally-defined ADHD.

METHODS

Eligibility Criteria

Studies included in this systematic review were peer-reviewed cross-sectional, prospective (including cohorts) or retrospective follow-up studies of subjects diagnosed with ADHD or dimensional symptoms and VP, VLBW, EP or ELBW. The search parameters included no initial cutoff date, and the final search was performed in April 2017. No publication language was ruled out.

Participants

We included studies with children, adolescents, and adults where one or more of the following conditions were assessed: VP, VLBW, EP or ELBW. Premature/low birth weight individuals must have been compared with a control group of subjects born near or at normal birth weight (NBW) (≥2,500 g) or near, at, or over 37 weeks of gestational age. Categorical ADHD diagnosis must have been established according to DSM-III, DSM-III-R, DSM-IV, or DSM-5 criteria, and Hyperkinetic Disorder (HKD) diagnosis was also accepted according to ICD-9 or ICD-10 criteria. Clinical assessment must have been performed either with validated diagnostic instruments (Online Appendix, Figure 1) or with validated scales for assessing ADHD symptoms and questions addressing other pertinent DSM or ICD criteria. To select adequate instruments to assess ADHD dimensionally, we accepted a list of scales included in a recently published Cochrane meta-analysis on the dimensional diagnosis of ADHD (18), added by two other instruments: the *Child Behavior Checklist* (CBCL) Attention Problem scale and the Hyperactivity scale of the *Strengths and Difficulties Questionnaire* (SDQ). These scales were included since they are part of the two best-known instruments for assessing psychopathology in children and adolescents, and their accuracy has been tested for ADHD symptomatology (19) (Online Appendix, Figure 2).

Information Sources

The bibliographic search included the PsycINFO, MEDLINE, EMBASE, and Cochrane databases. The search strategy for each database can be found in the

Online Appendix, Figure 3. Hand searches for published, unpublished and ongoing studies were performed by reviewing the bibliography section of the included full texts. We also e-mailed the most productive researchers in the field to obtain information on any ongoing or unpublished studies. If the author did not respond after two weeks, a second e-mail was sent.

Study Records

Data management. The studies were uploaded to the *Covidence* production platform (https://www.covidence.org/), where duplicates were identified and manually excluded. The data were extracted to a Google spreadsheet according to predefined criteria (described in this section) and independently entered by two authors.

Selection Process. The two-step online selection process began with title and abstract screening: three independent reviewers (A.P.F., G.U.B., and H.B) read the titles and abstracts, and included studies according to the inclusion/exclusion criteria. Any discrepancies were resolved among the reviewers. An independent reviewer (L.A.R.) acted as arbitrator whenever consensus could not be achieved. The process concluded with full text screening: four independent reviewers (A.P.F., G.U.B., H.B., and C.R.M.M.) working in pairs read the full text of the studies selected in step 1 to determine whether the inclusion criteria were met. At this point, any discrepancies were resolved among the reviewers. A third reviewer (L.A.R.) acted as arbitrator whenever consensus was not reached.

Data collection process:

Data were collected and double-checked by two reviewers (A.P.F. and C.R.M.M), with a third reviewer (L.A.R.) acting as arbitrator. When multiple reports from the same group of individuals were identified, the following inclusion criteria were used: 1st) the most complete data necessary for the meta-analysis; 2nd) age range for data collection (<18 years old); 3rd) larger sample size.

Whenever necessary, the authors were contacted by e-mail to resolve questions emerging from the extraction process or to request additional data. If no response was received from the corresponding author, a second message was sent after two weeks. If there was no response, we sent an e-mail to the senior author before discarding the study from the data collection process.

Included Data

We collected the following information from each selected study: first author and year of publication; country in which the sample was collected; place (i.e., hospital, neighborhood, or study sample name) and year of data collection; study design; presence of multiple births; mean age (weeks) and mean weight (grams) at birth; gender; mean age or age range at ADHD evaluation, severity of prematurity/underweight (i.e., whether VP, EP, VLBW or ELBW), information source (i.e. parents, teachers, or self-report); the name of the diagnostic instrument and ADHD rating scale; clinical/neurological and psychiatric comorbidities.

Study Factor and Outcomes

VP and VLBW were defined as gestational age less than 32 weeks and as birth weight less than 1,500 g, respectively (20). EP and ELBW are sub-groups of VP/VLBW with higher degrees of prematurity/low birth weight: less than 28 weeks and less than 1,000 g, respectively (20).

The primary outcome was categorically-defined ADHD. The diagnosis could have been established through structured diagnostic interviews with parents or adult subjects. The same procedure was applied to ADHD rating scales filled out by subjects, parents and/or teachers to collect data on ADHD dimensional symptoms.

Risk of Bias Assessment

All studies included for data extraction were independently assessed for bias. Two researchers (A.P.F. and C.R.M.M.) independently rated the studies according to a modified version of the Newcastle-Ottawa Scale (NOS) which assesses the quality of nonrandomized studies for systematic reviews and meta-analyses (21). A similar procedure was used in a recent publication (22). On its original scale, a study is judged from three major perspectives: (1) the selection of study groups, (2) the comparability of the groups, and (3) ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively (21). We used only the first two perspectives, since the third item was already part of the inclusion criteria for our review (see Online Appendix, Figure 4). All four sub-items of the “selection” perspective could receive a maximum score of one star, whereas “comparability” could receive two stars. Thus, each study could have received a minimum of zero (low quality and high risk of bias) and a maximum of 6 stars (high quality, low risk of bias).

Data Synthesis

Effect sizes were calculated as odds ratio (OR) with 95% confidence intervals (CI) for categorical data, according to the number of ADHD and non-ADHD subjects among the VP and/or VLBW, EP and/or ELBW and controls. To avoid zero-cases, the Cochrane Collaboration-recommended approach of including 0.5 was applied (23). For rating scales with continuous data, we calculated the standardized mean difference (SMD) with 95% CI. Given the expected diversity of methodology in the studies, we used the DerSimonian and Laird's random-effects models (24), which incorporate the effect of heterogeneity in the overall result to estimate the pooled effect sizes for both categorical and dimensional variables. When studies provided data from more than one information source (i.e. parents, teacher, and patients), *a priori* preference was given to parent data. To evaluate the effect of individual studies on effect size, the jackknife method was applied. Jackknife sensitivity analysis is a common procedure used in meta-analysis to test the stability of the outcomes. This is done by recalculating the effect size by removing a different study each time and then repeating the analyses (25). Heterogeneity was assessed with the I^2 statistic. To further evaluate the effects

of heterogeneity, we performed meta-regression analyses, examining the effects of age, article quality, the occurrence of multiple births, information source, country and rating scale. For the final multivariate meta-regression model, we selected only those co-variables associated with a $p \leq 0.2$ in univariate analyses (26). In addition, we evaluated publication bias using Egger's statistical test (27). Meta-analysis was computed in the R software meta-package (version 4.7-0) (28). Meta-regression analyses were performed in STATA 13.0.

RESULTS

Of 519 references identified in the literature search, 34 studies were included in the final analysis. Figure 1 presents the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (29) trial selection flowchart. Studies included in the final analysis are reported in Table 1 (Characteristics of studies included as categorical ADHD diagnosis for VP/VLBW or EP/ELBW) and Table 2 (Characteristics of studies included as ADHD rating scales with continuous data for VP/VLBW or EP/ELBW). The 94 full texts excluded from the final analysis and the reasons for their exclusion can be found in Online Appendix, Table 6. The most frequent reason for eligibility phase exclusion was "Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores" (N=37) (the list of instruments accepted for inclusion can be found in Figures 1 and 2 of the Online Appendix). E-mail correspondence with the most productive researchers in the field identified no ongoing or unpublished studies.

Seven studies (13, 30-35) were entered as both diagnostic instruments (categorical data) and rating scales (continuous data) in the meta-analysis. The EPICure Study was entered in both dimensional and categorical analyses, since the same population was assessed in different times and with distinct evaluation methods: Samara 2008 (36) (dimensional) and Johnson 2010 (37) (categorical). The same was done for the Central-West Canadian Cohort: Boyle 2011 (38) (dimensional) and Van Lieshout 2015 (39) (categorical). Woodward 2016 (35) was also entered in both categorical and dimensional analyses, since information from the dimensional scale,

Strengths and Difficulties Questionnaire (SDQ), was collected from the subjects at 2 years of age, and categorical diagnosis was performed at 9 years of age with the Development and Well-being Assessment (DAWBA). One publication (33) included two cohorts, but data were only available under request from the 2004 Pelotas cohort data managers. The “Rainbow Babies and Children's Hospital” name was given to two different cohorts. The participants were born between 1977 and 1979 for one (40), and between 1992 and 1995 for the other (41).

Twelve studies involving 1,787 subjects were included in the categorical diagnosis analysis. Subject mean age and birth weight ranged from 26 (34) to 30.6 (13) weeks, and from 818 (34) to 1320 g (13), respectively. Eight studies (13, 30, 32-35, 37, 42) reported patient assessment during childhood, three during adolescence (31, 43, 44), and one during adulthood (39). Five studies reported female predominance (32, 34, 39, 43, 44), 4 studies reported male predominance (13, 31, 35, 42), and 3 studies (30, 33, 37) did not report on gender.

Twenty-nine studies (3,504 individuals) were included for analysis of ADHD symptomatology according to ADHD rating scales. The age and birth weight ranged from 24.9 (45) to 31 weeks (46) and from 719 (47) to 1320 g (13), respectively. Twenty-three studies assessed ADHD during childhood (13, 30, 32-36, 41, 45, 46, 48-60), four during adolescence (31, 47, 61, 62) and two during adulthood (38, 40). We again found a predominance of females in the 15 studies (32, 34, 38, 40, 41, 46, 47, 51-54, 56-58, 61).

In both the categorical (Table 1) and the dimensional (Table 2) studies, clinical/neurological correlates and psychiatric comorbidities were only sporadically reported, so no further analysis could be performed.

Prematurity/birth weight and ADHD diagnosis

We found a significant risk of both VP/VLBW and EP/ELBW subjects to develop ADHD (pooled OR: 3.04; 95% CI, 2.19–4.21; I^2=17%, p=0.27), as shown in Figure 2. The subgroup analysis demonstrated that the more extreme the case, the higher the OR: VP/VLBW, OR: 2.25 (95% CI, 1.56–3.26), I^2=0%, p=0.82 and EP/ELBW, OR: 4.05

(95% CI, 2.38–6.87), I^2=34%, p=0.21. The subgroup analysis according to raters showed an OR: 3.13 (95% CI, 2.10–4.68), I^2=27%, p=0.20 for parents, and OR: 2.53 (95% CI, 1.31–4.89), I^2=0%, p=0.41 for patients (Online Appendix, Figure 5). No potential publication bias was found in this group of studies according to Egger's test, t=0.89 (p=0.39).

The sensitivity analysis is presented in the Online Appendix, Table 1. In the EP/ELBW group, the procedure did not change the OR significantly, but the exclusion of Burnett 2014 (43) and Scott 2012 (34) dropped the heterogeneity from 34% to 0% (p=0.50). In the overall analysis, there was no significant change in the OR, but the heterogeneity dropped from 17% (p=0.27) to 0% (p=0.56 and p=0.85) with the exclusion of Breeman 2016 (13) and Scott 2012 (34) respectively.

Prematurity/birth weight and ADHD symptomatology

The forest plot of the overall pooled SMD for inattention, H/I, and combined symptoms are presented in Figures 3 through 5. Compared to controls, the SMD was significantly higher for H/I (SMD:0.74; 95% CI, 0.35–1.13; I^2=95%, p<0.01), inattention (SMD: 1.31; 95% CI, 0.66–1.96; I^2=97%, p<0.01), and combined symptoms (SMD: 0.55; 95% CI, 0.42–0.68; I^2=81%, p<0.01), since no intervals crossed the zero axis. On the other hand, the comparison among the three dimensions is not significant, as all 95% CI are included in the same range, as demonstrated in figures 3, 4, and 5.

The overall heterogeneity was high for all three dimensions, except the combined dimension in the VP/VLBW group (moderate I^2=54%, p<0.01). No potential publication bias was found, as demonstrated by the Egger's test (t=2.10; p=0.07 and t=1.81; p=0.10 for inattention and H/I, respectively). However, a potential bias was detected for the combined dimension (t=2.38; p=0.02).

The sensitivity analysis for the combined presentation can be found in the Online Appendix, Table 2. The exclusion of Dahl 2006 (61) and Hack 2004 (40) reduced the heterogeneity from moderate to low levels in the VP/VLBW group. In the EP/ELBW group, the exclusion of Grunewaldt 2014 (51) reduced the heterogeneity

from 90% to 72%, while the study's exclusion reduced heterogeneity in the overall analysis from 81% (p<0.01) to 62% (p<0.01).

The most important modifications in the sensitivity analysis for H/I (Online Appendix, Table 3), were the lack of significance in the VP/VLBW analysis with the exclusion of Brogan 2014 (49), Hack 2004 (40), Hanke 2003 (52), Indredavik 2010 (31), and Levy-Shiff 1994 (62). The exclusion of Grunewaldt 2014 (51) reduced the heterogeneity from 92% (p<0.01) to 0% (p=0.45) in the EP/ELBW group. Regarding inattention (Online Appendix, Table 4), the exclusion of Brogan 2014 (49), Hack 2004 (40), and Indredavik 2010 (31) resulted in a lack of significance in the VP/VLBW analysis. Heterogeneity dropped from high to moderate after the exclusion of Grunewaldt 2014 (51) and Indredavik 2010 (31) in the EP/ELBW and VP/VLBW groups, respectively. The exclusions altered neither the significance of the overall SMD nor the heterogeneity in either dimension.

Meta-regression

A meta-regression was not performed for categorically-defined ADHD, since low heterogeneity was found in the meta-analysis of this group.

With respect to the ADHD rating scales, we performed individual analysis for continuous and categorical co-variables to better understand the heterogeneity. We included one co-variable into the model at a time for each of the ADHD symptom dimensions: age, article quality, country, occurrence of multiple births and information source (raters). As shown in the Online Appendix, Table 5, countries reaching a flexible p≤0.2 were to be included in a final multivariate meta-regression model; however, this was not feasible due to the lack of additional co-variables.

DISCUSSION

This systematic review and meta-analysis evaluated the risk of VP/VLBW (and EP/ELBW) individuals to develop ADHD, emphasizing well-defined categorical and dimensional diagnoses, and providing evidence of robust associations. Twelve

categorical diagnosis studies assessing a total of 1,787 subjects suggest that VP/VLBW and EP/ELBW individuals are about 3 times more likely to be diagnosed with ADHD than term-born controls. In the VP/VLBW group, this likelihood is approximately doubled, whereas in the EP/ELBW group it is increased fourfold. Furthermore, 29 studies on ADHD symptom, involving a total of 3,504 individuals, demonstrate that both inattention and H/I symptoms are similarly associated with VP/VLBW newborns, with large effect sizes found for the inattention and H/I dimensions and a moderate effect size for the total symptom scores.

Previous studies have suggested similar findings. A meta-analysis of the cognitive and behavioral outcomes of preterm-born school-aged children by Bhutta et al. (2002) (14) also found a significantly higher risk of ADHD diagnosis in preterm infants than controls (OR: 2.64, 95% CI, 1.85–3.78). In addition, they found that preterm children were at significant risk of reduced cognitive performance and other non-developmentally expected behaviors at school age. Interestingly, they found a gradient correlation, since gestational age and birth weight were directly proportional to the mean cognitive test scores. Moreover, Aarnoudse-Moens et al. (2009) (15), a meta-analysis on academic achievement, behavioral problems, and executive function, found that CBCL/TRF attention problems measured by teachers and parents were more pronounced in VP/VLBW children than in NBW controls. They also found a strong correlation between adverse outcomes and level of maturity at birth: smaller and more premature children were more prone to internalizing and externalizing behavior problems and poor academic achievement than heavier, more mature infants.

Our finding of higher ADHD risk in the EP/ELBW group than the VP/VLBW group endorses the idea of a gradient correlation (10-12) between prematurity/low birth weight and ADHD. Regarding the ADHD presentations, we found a similar risk for both inattentive and H/I types. Previous investigations have reported that EP had only a risk to develop the ADHD-inattentive type (37, 41) while others report risk for both ADHD inattentive and H/I (37, 48). Furthermore, we found a predominance of females in the VP/VLBW groups, although ADHD is typically associated with a high prevalence of males in the general population (63). Several studies have suggested that preterm born individuals with ADHD have phenotypic specificities which diverge from the non-

premature ADHD counterparts. These include a predominance of inattention symptoms, less psychiatric comorbidity (64, 65), higher diagnostic stability from childhood to adulthood (13), more perinatal clinical/neurological complications, and major disabilities (13, 15, 43, 66, 67). In addition, the preponderance of males, which is typically seen in non-premature ADHD, was also not observed in preterm subjects (64).

Despite the fact that both clinical/neurological and psychiatric comorbidities were reported in some of the studies, further analyses were not possible due to the heterogeneity of the data described. It is important to note that our findings suggesting a robust risk of VP/VLBW subjects to develop ADHD are similar to those found in other behavioral and psychiatric disorders. In a previous meta-analysis, Burnett et al. (2011) (68) showed that a prevalence of any psychiatric diagnosis in preterm/LBW individuals was 3.66 times higher (95% CI, 2.57–5.21) than NBW controls. Similarly, they found a high risk for anxiety or depressive disorder (OR: 2.86; 95% CI, 1.73–4.73), although the study did not provide data on ADHD or other psychiatric diagnoses. Another meta-analysis (69) found a significant association between autism diagnosis and LBW, but not preterm birth. The reasons for increased vulnerability to ADHD, behavioral and psychiatric problems in preterm birth/low birth weight individuals remain unknown but a number of hypotheses have been put forward, including pre- and post-natal adversities, such as the environmental problems they must face, as well as parental and biological issues such as hypothalamic–pituitary–adrenal axis dysregulations and perinatal systemic inflammation, which could cause structural and functional brain disorders such as ADHD and other psychiatric and developmental disorders (17, 68, 70-72).

Certain limitations should be considered when interpreting our findings. First, potentially important articles were excluded during the eligibility phase for not using validated diagnostic instruments or the rating scales selected in our protocol. Second, many studies were excluded due to different data definitions (i.e. different categorizations for prematurity/birth-weight levels). Third, although excluding grey literature from our review may have led to the over-representation of studies with statistically significant findings (73), a recent systematic review from the OPEN

consortium (74) demonstrated that the exclusion of such studies has a negligible impact on effect sizes. Fourth, the heterogeneous reporting of clinical/neurological correlates in VP/VLBW individuals precluded us from comparing those that did and did not develop ADHD for these variables. Fifth, substantially high heterogeneity was found for all three ADHD dimensions, indicating that there is clinical or methodological diversity among studies (23). It is important to note that potential explanatory variables (age, article quality, country, occurrence of multiple births and information source) entered in meta-regression analyses could not explain such variability. Sixth, our analyses included studies spanning a 30-year period (1977-2007). Although the lack of publication date limits increased the number of subjects in the analysis, the VP/VLBW subjects might not have the same perinatal profile over time, given the advances in care management (75). Such a limitation was also reported in Bhutta's 2002 meta-analysis (14). Moreover, we also assumed that the different classification systems and versions (DSM-III, DSM-III- R, DSM-IV, DSM-5, ICD-9 or ICD-10) had similar ADHD diagnostic performance. Seventh, the ADHD risk found in our meta-analysis adequately represents the risk in high-income countries, but cannot be generalized to middle/low-income countries. Among the 34 included studies, only the 2004 Pelotas cohort (33) came from a middle-income country. In middle/low-income countries, the risk mechanisms could vary due to different determinant profiles (33). As for the strengths of our review, we performed a broad literature search of cohort, case-control, and cross-sectional studies with no language restriction, allowing us to find a substantial number of articles. Most importantly, our strict inclusion criteria allowed only studies with well-defined ADHD categorical diagnosis in the meta-analyses, unlike previous systematic reviews and meta-analyses (14, 15).

CONCLUSION

In conclusion, our findings provide robust evidence that VP/VLBW individuals have an increased risk of ADHD both in categorical and dimensional analyses, and there is an even stronger association in the EP/ELBW group. In terms of clinical applicability, our findings suggest that premature infants need specific neonatology,

pediatric and psychiatric prevention and management interventions to minimize the ADHD burden. Future research in this field should clarify specific causal determinants associated with prematurity and low birth weight that could lead to the development of ADHD.

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References

1. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. *Seminars in fetal & neonatal medicine.* Apr 2016;21(2):68-73.

2. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet.* Jun 09 2012;379(9832):2162-2172.

3. Linnet KM, Wisborg K, Agerbo E, Secher NJ, Thomsen PH, Henriksen TB. Gestational age, birth weight, and the risk of hyperkinetic disorder. *Archives of disease in childhood.* Aug 2006;91(8):655-660.

4. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author.

5. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of child psychology and psychiatry, and allied disciplines.* Mar 2015;56(3):345-365.

6. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *The American journal of psychiatry.* Jun 2007;164(6):942-948.

7. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *The British journal of psychiatry : the journal of mental science.* Mar 2009;194(3):204-211.

8. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC medicine.* Sep 04 2012;10:99.

9. Langley K, Fowler T, Ford T, et al. Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. *The British journal of psychiatry : the journal of mental science.* Mar 2010;196(3):235-240.

10. Anderson P, Doyle LW, Victorian Infant Collaborative Study G. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. *Jama.* Jun 25 2003;289(24):3264-3272.

11. Horwood LJ, Mogridge N, Darlow BA. Cognitive, educational, and behavioural outcomes at 7 to 8 years in a national very low birthweight cohort. *Archives of disease in childhood. Fetal and neonatal edition.* Jul 1998;79(1):F12-20.

12. Sucksdorff M, Lehtonen L, Chudal R, et al. Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/ Hyperactivity Disorder. *Pediatrics.* Sep 2015;136(3):e599-608.

13. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. Attention problems in very preterm children from childhood to adulthood: the Bavarian Longitudinal Study. *Journal of child psychology and psychiatry, and allied disciplines.* Feb 2016;57(2):132-140.

14. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *Jama.* Aug 14 2002;288(6):728-737.

15. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics.* Aug 2009;124(2):717-728.

16. Thapar A, Cooper M, Jefferies R, Stergiakouli E. What causes attention deficit hyperactivity disorder? *Archives of disease in childhood.* Mar 2012;97(3):260-265.

17. O'Shea TM, Downey LC, Kuban KK. Extreme prematurity and attention deficit: epidemiology and prevention. *Frontiers in human neuroscience.* 2013;7:578.

18. Storebo OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *The Cochrane database of systematic reviews.* Nov 25 2015(11):CD009885.

19. Chang LY, Wang MY, Tsai PS. Diagnostic Accuracy of Rating Scales for Attention-Deficit/Hyperactivity Disorder: A Meta-analysis. *Pediatrics.* Mar 2016;137(3):e20152749.

20. Tucker J, McGuire W. Epidemiology of preterm birth. *Bmj.* Sep 18 2004;329(7467):675-678.

21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 10, 2015.

22. Rotenstein LS, Ramos MA, Torre M, et al. Prevalence of Depression, Depressive Symptoms, and Suicidal Ideation Among Medical Students: A Systematic Review and Meta-Analysis. *Jama.* Dec 06 2016;316(21):2214-2236.

23. Higgins JPT, Green S (editors). Studies with zero-cell counts. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration website. http://handbook.cochrane.org/chapter_16/16_9_2_studies_with_zero_cell_counts.htm. 2011. Accessed April 5, 2017.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials.* Sep 1986;7(3):177-188.

25. Miller RG. The Jackknife--A Review. *Biometrika.* Apr 1974;61(1):1-15.

26. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *American journal of epidemiology.* Dec 01 1993;138(11):923-936.

27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* Sep 13 1997;315(7109):629-634.

28. Schwarzer G. meta: An R package for meta-analysis. *R News.* 2007;7(3):40-45.

29. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology.* Oct 2009;62(10):e1-34.

30. Hatch B, Healey DM, Halperin JM. Associations between birth weight and attention-deficit/hyperactivity disorder symptom severity: indirect effects via primary neuropsychological functions. *Journal of child psychology and psychiatry, and allied disciplines.* Apr 2014;55(4):384-392.

31. Indredavik MS, Vik T, Evensen KA, Skranes J, Taraldsen G, Brubakk AM. Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. *Journal of developmental and behavioral pediatrics : JDBP.* May 2010;31(4):286-294.

32. McNicholas F, Healy E, White M, et al. Mental health outcomes at age 11 of very low birth weight infants in Ireland. Irish Journal of Psychological Medicine. 2016;33(2):93-104. doi:10.1017/ipm.2015.25.

33. Murray E, Pearson R, Fernandes M, et al. Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison between high-income and middle-income cohorts. *Journal of epidemiology and community health.* Jul 2016;70(7):704-709.

34. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. *Journal of developmental and behavioral pediatrics : JDBP.* Apr 2012;33(3):202-213.

35. Woodward LJ, Lu Z, Morris AR, Healey DM. Preschool self regulation predicts later mental health and educational achievement in very preterm and typically developing children. *The Clinical neuropsychologist.* Feb 2017;31(2):404-422.

36. Samara M, Marlow N, Wolke D, Group EPS. Pervasive behavior problems at 6 years of age in a total-population sample of children born at </= 25 weeks of gestation. *Pediatrics.* Sep 2008;122(3):562-573.

37. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *Journal of the American Academy of Child and Adolescent Psychiatry.* May 2010;49(5):453-463 e451.

38. Boyle MH, Miskovic V, Van Lieshout R, et al. Psychopathology in young adults born at extremely low birth weight. *Psychological medicine.* Aug 2011;41(8):1763-1774.

39. Van Lieshout RJ, Boyle MH, Saigal S, Morrison K, Schmidt LA. Mental health of extremely low birth weight survivors in their 30s. *Pediatrics.* Mar 2015;135(3):452-459.

40. Hack M, Youngstrom EA, Cartar L, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. *Pediatrics.* Oct 2004;114(4):932-940.

41. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. *Journal of developmental and behavioral pediatrics : JDBP.* Apr 2009;30(2):122-130.

42. Treyvaud K, Ure A, Doyle LW, et al. Psychiatric outcomes at age seven for very preterm children: rates and predictors. *Journal of child psychology and psychiatry, and allied disciplines.* Jul 2013;54(7):772-779.

43. Burnett A, Davey CG, Wood SJ, et al. Extremely preterm birth and adolescent mental health in a geographical cohort born in the 1990s. *Psychological medicine.* May 2014;44(7):1533-1544.

44. Cooke RW, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. *Archives of disease in childhood. Fetal and neonatal edition.* Sep 1999;81(2):F116-121.

45. Mansson J, Stjernqvist K, Backstrom M. Behavioral outcomes at corrected age 2.5 years in children born extremely preterm. *Journal of developmental and behavioral pediatrics : JDBP.* Sep 2014;35(7):435-442.

46. Torrioli MG, Frisone MF, Bonvini L, et al. Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities. *Brain & development.* May 2000;22(3):163-168.

47. Grunau RE, Whitfield MF, Fay TB. Psychosocial and academic characteristics of extremely low birth weight (< or =800 g) adolescents who are free of major impairment compared with term-born control subjects. *Pediatrics.* Dec 2004;114(6):e725-732.

48. Anderson PJ, De Luca CR, Hutchinson E, et al. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. *Developmental neuropsychology.* 2011;36(1):57-73.

49. Brogan E, Cragg L, Gilmore C, Marlow N, Simms V, Johnson S. Inattention in very preterm children: implications for screening and detection. *Archives of disease in childhood.* Sep 2014;99(9):834-839.

50. de Kieviet JF, van Elburg RM, Lafeber HN, Oosterlaan J. Attention problems of very preterm children compared with age-matched term controls at school-age. *The Journal of pediatrics.* Nov 2012;161(5):824-829.

51. Grunewaldt KH, Fjortoft T, Bjuland KJ, et al. Follow-up at age 10 years in ELBW children - functional outcome, brain morphology and results from motor assessments in infancy. *Early human development.* Oct 2014;90(10):571-578.

52. Hanke C, Lohaus A, Gawrilow C, Hartke I, Kohler B, Leonhardt A. Preschool development of very low birth weight children born 1994-1995. *European journal of pediatrics.* Mar 2003;162(3):159-164.

53. Leijon I, Ingemansson F, Nelson N, Wadsby M, Samuelsson S. Reading deficits in very low birthweight children are associated with vocabulary and attention issues at the age of seven. *Acta paediatrica.* Jan 2016;105(1):60-68.

54. Nadeau L, Boivin M, Tessier R, Lefebvre F, Robaey P. Mediators of behavioral problems in 7-year-old children born after 24 to 28 weeks of gestation. *Journal of developmental and behavioral pediatrics : JDBP.* Feb 2001;22(1):1-10.

55. Perkinson-Gloor N, Hagmann-von Arx P, Brand S, et al. The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood. *Journal of psychiatric research.* Jan 2015;60:141-147.

56. Shum D, Neulinger K, O'Callaghan M, Mohay H. Attentional problems in children born very preterm or with extremely low birth weight at 7-9 years. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists.* Jan 2008;23(1):103-112.

57. Stjernqvist K, Svenningsen NW. Ten-year follow-up of children born before 29 gestational weeks: health, cognitive development, behaviour and school achievement. *Acta paediatrica.* May 1999;88(5):557-562.

58. Sykes DH, Hoy EA, Bill JM, McClure BG, Halliday HL, Reid MM. Behavioural adjustment in school of very low birthweight children. *Journal of child psychology and psychiatry, and allied disciplines.* Mar 1997;38(3):315-325.

59. Teplin SW, Burchinal M, Johnson-Martin N, Humphry RA, Kraybill EN. Neurodevelopmental, health, and growth status at age 6 years of children with birth weights less than 1001 grams. *The Journal of pediatrics.* May 1991;118(5):768-777.

60. Huang JH, Huang HL, Chen HL, Lin LC, Tseng HI, Kao TJ. Inattention and development of toddlers born in preterm and with low birth weight. *The Kaohsiung journal of medical sciences.* Jul 2012;28(7):390-396.

61. Dahl LB, Kaaresen PI, Tunby J, Handegard BH, Kvernmo S, Ronning JA. Emotional, behavioral, social, and academic outcomes in adolescents born with very low birth weight. *Pediatrics.* Aug 2006;118(2):e449-459.

62. Levy-Shiff R, Einat G, Mogilner MB, Lerman M, Krikler R. Biological and environmental correlates of developmental outcome of prematurely born infants in early adolescence. *Journal of pediatric psychology.* Feb 1994;19(1):63-78.

63. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 19 2016;387(10024):1240-1250.

64. Johnson S, Wolke D. Behavioural outcomes and psychopathology during adolescence. *Early human development.* Apr 2013;89(4):199-207.

65. Johnson S, Kochhar P, Hennessy E, Marlow N, Wolke D, Hollis C. Antecedents of Attention-Deficit/Hyperactivity Disorder Symptoms in Children Born Extremely Preterm. *Journal of developmental and behavioral pediatrics : JDBP.* May 2016;37(4):285-297.

66. Anderson PJ, Doyle LW, Victorian Infant Collaborative Study G. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics.* Jul 2004;114(1):50-57.

67. Johnson S. Cognitive and behavioural outcomes following very preterm birth. *Seminars in fetal & neonatal medicine.* Oct 2007;12(5):363-373.

68. Burnett AC, Anderson PJ, Cheong J, Doyle LW, Davey CG, Wood SJ. Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. *Psychological medicine.* Dec 2011;41(12):2463-2474.

69. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics.* Aug 2011;128(2):344-355.

70. Dammann O, O'Shea TM. Cytokines and perinatal brain damage. *Clinics in perinatology.* Dec 2008;35(4):643-663, v.

71. Hagberg H, Peebles D, Mallard C. Models of white matter injury: comparison of infectious, hypoxic-ischemic, and excitotoxic insults. *Mental retardation and developmental disabilities research reviews.* 2002;8(1):30-38.

72. Coghill D, Nigg J, Rothenberger A, Sonuga-Barke E, Tannock R. Whither causal models in the neuroscience of ADHD? *Developmental science.* Mar 2005;8(2):105-114.

73. Conn VS, Valentine JC, Cooper HM, Rantz MJ. Grey literature in meta-analyses. *Nursing research.* Jul-Aug 2003;52(4):256-261.

74. Schmucker CM, Blumle A, Schell LK, et al. Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research. *PloS one.* 2017;12(4):e0176210.

75. Johnston MV, Fatemi A, Wilson MA, Northington F. Treatment advances in neonatal neuroprotection and neurointensive care. *The Lancet. Neurology.* Apr 2011;10(4):372-382.

76. Stjernqvist K, Svenningsen NW. Extremely low-birth-weight infants less than 901 g: development and behaviour after 4 years of life. *Acta paediatrica.* May 1995;84(5):500-506.

77. Lindstrom K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics.* Jan 2009;123(1):e47-53.

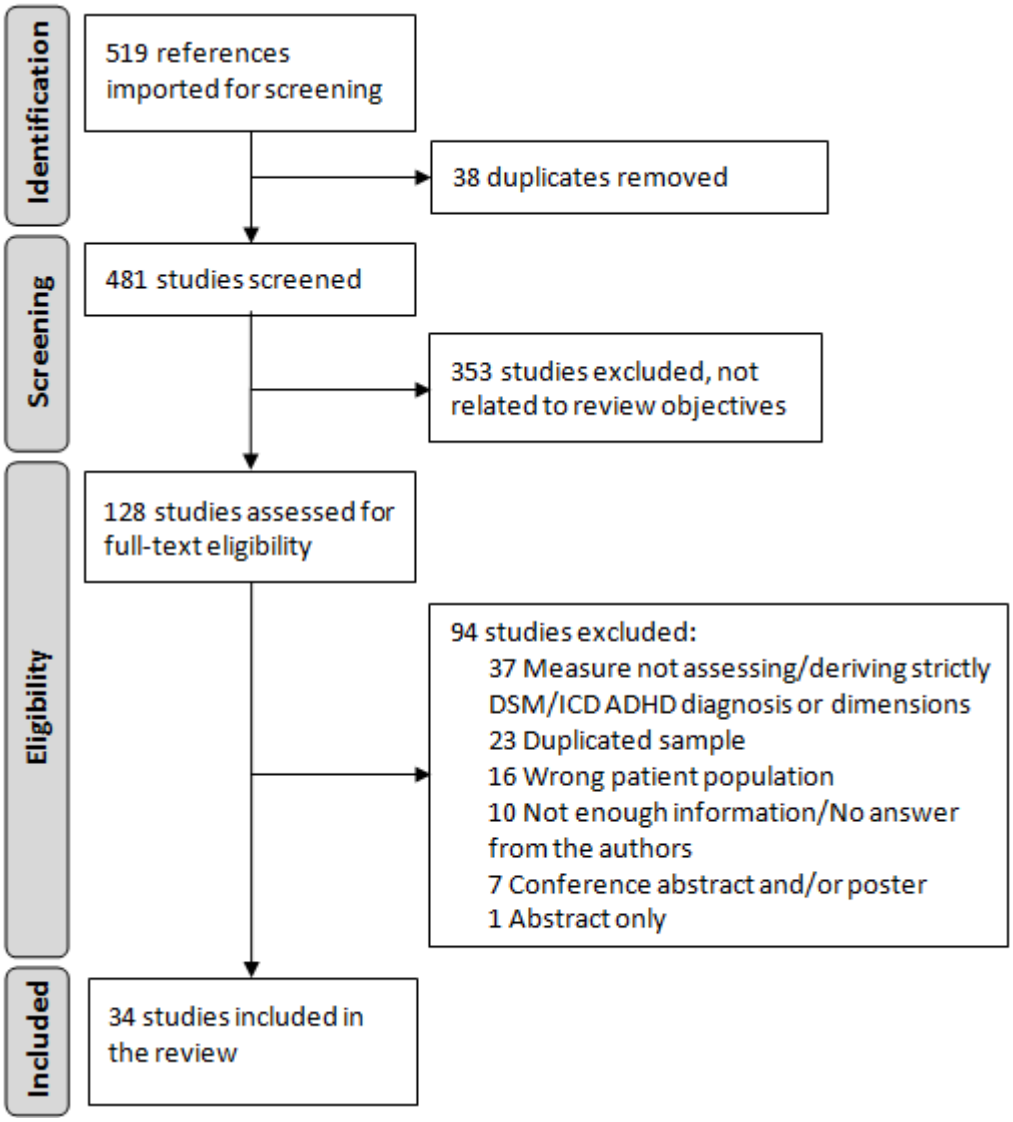


FIGURE 1: Study selection flowchart.

TABLE 1: Characteristics of studies included as categorical ADHD diagnosis for VP/VLBW or EP/ELBW.

Author, year	Sample (year of birth)	Country	N	Age mean at birth (weeks; mean or range)	Weight mean at birth (g)	Age at evaluation (years; mean or range)	Male (%)	Scale	Rater	Clinical/Neurological Comorbidities (n (%))	Psychiatric Comorbidities (n (%))	NOS	
												Case-control	Cohort
Breeman, 2016[13 a]	The Bavarian Longitudinal Study 1985–1986	Germany	260	30.6	1320	06/ago	53.1	MPI	Parents	SGA: 108 (41.5%); Sev.D: 50 (19.2%)	NS	-	5
Burnett, 2014[43]	Victorian Infant Collaborative Study Group (1991-1992)	Australia	215	26.6	1218	17.9	45	ChIPS	Subject	MNBI: 22 (10%); SGA: 34 (16%) PCU: 31 (67%)	MDD: 28 (14%); BP: 1 (0.5%); DD: 6 (3%); GAD: 10 (5%); Soc.P: 2 (1%); Spe.P: 8 (4%); PTSD: 3 (1%); PD: 5 (2%); Agoraphobia: 1 (0.5%); OCD: 4 (2%)	4	-
Cooke, 1999[44]	Liverpool Maternity Hospital, January 1980 - June 1981	UK	87	28.6	1103	13	46	CAPA	Parents	PVH: 19 (21.8%), MCL: 2 (2.2%); Convulsions: 7 (8%); PBC: 22 (25.2%)	NS	-	4

Hatch, 2014[30 a]	New York City metropolitan area	USA	197	NS	978.06	03/abr	NS	K-SADS-PL	Parents	NS	NS	4	-
Indredavik, 2010[31 a]	University Hospital in Trondheim (1986–1988)	Norway	65	29	1180	14	54	K-SADS-PL	Parents	IVH: 11 (4%)	NS	5	-
Johnson, 2010[37 b]	EPICure Study - UK and Ireland (March - December 1995)	UK	219	≤ 26	NS	11	NS	DAWBA	Parents	NS	Aut.D: 16 (8%); SAD: 5 (2.5%); Spe.P: 3 (1.5%); Soc.P: 1 (0.5%); PTSD: 1 (0.5%); GAD: 4 (2%); MD: 3 (1.5%); ODD: 11 (5%); CD: 1 (0.5%); TD: 2 (1%)	-	5
McNicholas, 2015[32 a]	Dublin Maternity Hospital born (1995-1996)	Ireland	64	30	1172	11.6	37.5	DAWBA	Parents	IVH: 12(18.7%), ACU: 40 (62.5%)	ADNE: 8 (12.5%); CD: 1 (1.5%); Asp.D: 3 (4.6%)	-	4
Murray, 2016[33 a,c]	2004 Pelotas Cohort	Brazil	48	≤ 32	≤ 1500	6.7	NS	DAWBA	Parents	NS	NS	-	5
Scott, 2012[34 a]	Rainbow Babies and Children's	USA	148	26	818	5.96	46	P-ChIPS	Parents	NS	ODD: 27 (19%) CD: 8 (6%)	-	5

	Hospital (2001–2003)										Soc. P: 9 (6%) Spe. P: 24 (6%) SAD: 8 (6%) GAD: 4 (3%)		
Treyvaud, 2013[42]	Victorian Infant Brain Studies, 2001 to 2003	Australia	177	27.5	975	7	53	DAWBA	Parents	SGA: 16 (9%), GBA: 117 (66.1%), NDD: 9 (5.08%)	SAD: 6 (3%); Spe. P: 7 (4%); GAD: 4 (2%); Depression: 1 (0.5%); ODD: 3 (2%)	-	4
Van Lieshout, 2015[39 d]	Central-west Ontario (1977-1982)	Canada	84	27.05	829	32.02	37	MINI	Subject	SGA: 26 (31%); ACU: 46 (39%)	Anx.D: 14 (16.6%); AB: 7 (8.3%); APP: 17 (20.2%); Depression 13 (15.4%)	-	4
Woodward, 2016[35 a]	Christchurch Women's Hospital, November 1998 to December 2000	New Zealand	223	27.81	1054.4	9	51	DAWBA	Parents	MSWMA: 17(17%), IVH Grade 3-4: 6 (6%), SPNE: 7 (7%)	CD 7 (7%), Anx.D: 7 (7%), Depression 3 (3%), ASD: 3 (3%)	-	6

AB: Antisocial Behaviour; ACU: Antenatal Corticosteroid Use; ADNE: Anxiety Disorders (Not Specified); Anx.D: Anxiety Disorder; APP: Avoidant Personality Problems; ASD: Autism Spectrum Disorder; Asp.D: Asperger's Disorder; Aut.D: Autistic Disorder; BP: Bipolar Disorder; CD: Conduct Disorder; ChIPS: Cohen-Hoberman Inventory of Physical Symptoms; DAWBA: Development and Well-Being Assessment; DD: Dysthymic Disorder; EPICure: Extremely Premature Infants Cure; GAD: Generalized Anxiety Disorder; GBA: Global Brain Abnormality; IQ: Intelligence Quotient; IVH: Intraventricular Hemorrhage; K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; MCL: Minor Cystic Leukomalacia; MDD: Major Depressive Disorder; MINI: International Neuropsychiatric Interview; MNBI: Major neonatal brain injury; MPI: Mannheim Parent Interview; MSWMA: Moderate to Severe White Matter Abnormality; N: Number of subjects; NDD: Neurodevelopmental Disability; NOS: Newcastle-Ottawa Scale; NS: Not stated; OCD: Obsessive–Compulsive Disorder; ODD: Oppositional Defiant Disorder; PBC: Positive Blood Culture ; P-ChIPS: Children's Interview for Psychiatric Syndromes-Parent Version; PCU: Postnatal Corticosteroid Use; PD: Panic Disorder; PTSD: Posttraumatic Stress Disorder; PVH: Periventricular Hemorrhage; SAD: Separation Anxiety Disorder; Sev.D: Severe Disability (IQ≤2 SD, Cerebral Palsy Grade 3 or 4, or Blindness/Deafness); SD: standard Deviation; SGA: Small for Gestational Age; Soc.P: Social Phobia; Spe.P: Specific Phobia; SPNE: Suspected or Proven Necrotizing Enterocolitis; TD: Tic Disorder; UK: United Kingdom; USA: United States of America.

[a] These studies also contributed with data from ADHD rating scales for the meta-analysis of dimensional data.
[b] Results of this study are also reported in Samara 2008.[36]
[c] Results for the Pelotas Cohort were obtained after requirement. Contacts with the Avon Longitudinal Study of Parents and Children (ALSPAC) investigators were not successful.
[d] Results of this study are also reported in Boyle 2011.[38]

TABLE 2: Characteristics of studies included as ADHD rating scales with continuous data for VP/VLBW or EP/ELBW.

Author, year	Sample (year of birth)	Country	N	Age mean at birth (weeks; mean or range)	Weight mean at birth (g)	Age at evaluation (years; mean or range)	Male (%)	Scale	Rater	Clinical/ neurological comorbidities (n (%))	Psychiatric comorbidities (n (%))	NOS	
												Case-control	Cohort
Anderson, 2011[48]	State of Victoria (January to December, 1997)	Australia	189	26.5	833	8.1	NS	Conners	Parents	CP: 22(12%); IVH Grade 3-4: 7(4%); CPL: 6(3%); NE: 10(5%); RP: 97(51%); BD: 119(63%); ACU: 166 (88%); PCU: 70 (37%)	NS	-	5
Boyle, 2011[38 a]	Central-west Ontario (1977-1982)	Canada	142	26.8	835	23.2	43.7	Barkley, YASR	Subject	SGA: 35 (26.8%); NI: 23 (27%)	NS	-	4
Breeman, 2016[13 b]	The Bavarian Longitudinal Study (1985–1986)	Germany	260	30.6	1320	06/ago	53.1	CBCL	Parents	SGA: 108 (41.5%); Sev. D: 50(19.2%)	NS	-	5
Brogan, 2014[49]	Premature Infants' Skills in Mathematic	UK	117	28.6	1218	9.7	55	DuPaul ADHD-RS, SDQ	Parents, Teacher	NS	NS	4	-

	s (PRISM) study (September 2001 to August 2003)												
Dahl, 2006[61]	Two counties of Norway (1998-2004)	Norway	99	29.3	1188	13-18	44.4	CBCL, YSR	Parents, subject	CP: 8(8.1%); IVH Grade 3-4: 2(3.9%); BD: 11(13.6%); Sepsis: 10(10.1%); PDA: 13(13.3%)	NS	4	-
de Kieviet, 2012[50]	VU University Medical Center Amsterdam (September, 2001 to July, 2003)	The Netherlands	66	29.3	1241	7.5	50	CBCL	Parents	SGA: 18 (27.3%); Sepsis: 42(63.6%); BD: 19(28.8%); IVH: 14(21.2%) ACU: 53 (80.3%)	NS	5	-
Grunau, 2004[47]	British Columbia's Children's Hospital (January, 1981 to February, 1986)	Canada	53	25.8	719	17.3	32	CBCL	Parents	SGA: 9 (17%)	NS	5	-
Grunewaldt, 2014[51]	Trondheim University	Norway	31	26.1	773	10.2	48	ADHD-RS	Parents	IVH: 11(47%);	NS	-	4

	Hospital (1999–2001)									Sepsis: 7(30.4%); PDA: 7(30%) ACU: 18 (58%%) PCU: 12 (39%)			
Hack, 2004[40]	Rainbow Babies and Children's Hospital (1977–1979)	USA	241	29.7	1179.51	20	48.1	ADHD-RS, YASR	Parents, subject	NS	NS	-	4
Hack, 2009[41]	Rainbow Babies and Children's Hospital (1992–1995)	USA	219	26.4	810	8	41	CSI-4	Parents	BD: 93(43%); Sepsis: 108(49%); NE: 11(5%); IVH or PL: 51(23%)	ODD: 12(6%); CD: 19(9%); GAD: 7(3%); MDD: 4(2%); Aut.D: 4(2%); Asp.D: 3(1%); Soc.P: 16(7%); SAD: 9(4%); Spe. P: 108(50%)	5	-
Hanke, 2003[52]	Department of Paediatrics in Marburg (January, 1994 to	Germany	60	29	1124	6.2	45	CBCL, HKS	Parents	SGA: 11 (18.3%); IVH: 16(26.6%); BD: 20(33.3%)	NS	4	-

	December, 1996)												
Hatch, 2014[30 b]	New York City metropolitan area	USA	197	NS	978.06	03/abr	NS	ADHD-RS	Parents, Teacher	NS	NS	4	-
Huang, 2012[60]	Kaohsiung Medical University Hospital and Kaohsiung Municipal Hsiao-Kang Hospital	Taiwan	20	28.95	<1500	2	64	DBRS-Toddler	Parents	0	0	3	-
Indredavik, 2010[31 b]	University Hospital in Trondheim (1986–1988)	Norway	65	29	1180	14	54	ADHD-RS	Parents	SGA: 24 (37%); CP: 8(12%); IVH: 11(4%)	NS	5	-
Leijon, 2016[53]	South-east region of Sweden (January, 1998 - December, 1998)	Sweden	51	28.8	1105	7.8	37.2	CBCL	Parents	BD: 14(27%); RDS: 23(45%); Sepsis: 14(28%); SGA: 29 (27%);IVH: 1(2%); PL: 2(5%); RP: 2(4%)	NS	5	-
Levy-Shiff, 1994[62]	Kaplan Hospital and Beilinson Hospital	Israel	90	29	1190	13.3	NS	Conners	Parents	NS	NS	1	-

Månsson, 2014[45]	EXPRESS (April, 2004 - March, 2007)	Sweden	344	24.9	780	2.5	54.7	CBCL	Parents	SGA: 62 (18%); CP: 21(6,1%); IVH: 30(8.7%); PL: 14(4.1%); BD: 80(23.2%); NE: 18(5.2%); RP 115(33.4%)	NS	4	-
McNicholas, 2015[32 b]	Dublin Maternity Hospital (1995-1996)	Ireland	64	30	1172	11.6	38	SDQ	Parents, subject, teachers	IVH: 12(18.7%)	ADNS: 8(12.5%); CD: 1(1.5%); Asp.D: 3(4.6%)	-	4
Murray, 2016[33 b, c]	2004 Pelotas Cohort	Brazil	48	≤ 32	≤ 1500	6.7	NS	SDQ	Parents	NS	NS	-	5
Nadeau, 2001[54]	Ste-Justine Hospital (January, 1987 - October, 1990)	Canada	61	27.4	1024.3	7	49	CBCL, TRF	Parents, teachers	NS	NS	4	-
Perkinson-Gloor, 2015[55]	University Children's Hospital Basel (June, 2001 - December, 2005)	Switzerland	58	29.7	1302.1	8.2	69	SDQ	Parents	RDS: 45(77.6%); AP: 46(79.3%); BD: 3(5.2%)	NS	-	3

Samara, 2008[36 d]	EPICure Study (March through December 1995)	UK	241	<=25	740	6	50.2	SDQ	Parents, teachers	CP: 41(17.4%); VM: 76(31.5%)	NS	-	5
Scott, 2012[34 b]	Rainbow Babies and Children's Hospital (2001–2003)	USA	148	26	818	5.96	46	CBCL	Parents	NS	ODD: 27(19%); CD: 8(6%); Spe.P: 24(6%); Soc.P: 9(6%); SAD: 8(6%); GAD: 4(3%)	-	5
Shum, 2008[56]	Mater Children's Hospital	Australia	45	26.4	838.2	07/set	48.8	ADHD-RS	Parents, teachers	NS	NS	3	-
Stjernqvist, 1999[57]	Southern Swedish population, (1985–1986)	Sweden	65	27.1	1042	10.5	41	CBCL	Parents	SGA: 9 (15%); IVH: 13(21%); BD: 11(18%)	NS	5	-
Sykes, 1997[58]	Royal Maternity Hospital (1978-1981)	Ireland	243	30.4	1272	7.43	41	TRF	Teachers	IVH: 6(3%)	NS	2	-
Teplin, 1991[59]	Neonatal intensive care unit of the University of North Carolina Hospitals, 1980	USA	28	28	905	6.2	50	Conners	Parents	SGA: 10 (37%); MSD: 3(12%); VI: 3(12%); HL: 2(7%)	NS	4	-

Torrioli, 2000[46]	Policlinico Gemelli (1991-1993)	Italy	36	31	1120	4.9	41.6	Conners	Parents	NS	NS	1	-
Woodward, 2016[35 b]	Christchurch Women's Hospital, November 1998 to December 2000	New Zealand	223	27.81	1054.4	2	51	SDQ	Parents	MSWMA: 17(17%), IVH Grade 3-4: 6 (6%), SPNE: 7 (7%)	CD 7 (7%), Anx.D: 7 (7%), Depression 3 (3%), ASD: 3 (3%)	-	6

AB: Antisocial Behavior; ACU: Antenatal Corticosteroid Use; ADHD: Attention Deficit Hyperactivity Disorder; ADHD-RS: ADHD rating scale-IV; ADNS: Anxiety Disorders (Not Specified); AP: Apnea of Prematurity; APP: Avoidant Personality Problems; Asp.D: Asperger's Disorder; Aut.D: Autistic Disorder; BD: Bronchopulmonary Dysplasia; CBCL: Child Behavior Checklist; CD: Conduct Disorder; CP: Cerebral Palsy; CPL: Cystic Periventricular Leukomalacia; CSI-4: Child Symptom Inventory-4; DBRS-Toddler: Disruptive Behaviour Rating Scale; GAD: Generalized Anxiety Disorder; HL: Hearing Loss; HKS: Questionnaire of Hyperactivity Symptoms; IVH: Intraventricular Haemorrhage; MDD: Major Depressive Disorder; MSD: Mild Spastic Diplegia; MSWMA: Moderate to Severe White Matter Abnormality; NE: Necrotizing Enterocolitis; NI: Neurosensory Impairment; NOS: Newcastle-Ottawa Scale; ODD: Oppositional Defiant Disorder; PCU: Postnatal Corticosteroid Use; PDA: Patent Ductus Arteriosus; PL: Periventricular Leukomalacia; PTSD: Posttraumatic Stress Disorder; RDS: Respiratory Distress Syndrome; RP: Retinopathy of Prematurity; SAD: Separation Anxiety Disorder; Sev.D: Severe disability (IQ≤2 SD, Cerebral Palsy Grade 3 or 4, or Blindness/Deafness); SDQ: Strengths and Difficulties Questionnaire; SGA: Small for Gestational Age; Soc.P: Social Phobia; Spe.P: Specific Phobia; SPNE: Suspected or Proven Necrotizing Enterocolitis; TD: Tic Disorder; TRF: Teacher Report Form; UK: United Kingdom; USA: United States of America; VI: Visual Impairments; VM: Ventriculomegaly; YASR: Young Adult Self-Report and Young Adult Behavior Checklist; YSR: Youth Self-Report

[a] Results of this study are also reported in Van Lieshout 2015[39]

[b] These studies also contributed with data from ADHD rating scales for the meta-analysis of categorical data.

[c] Results for the Pelotas Cohort were obtained after requirement. Contacts with the Avon Longitudinal Study of Parents and Children (ALSPAC) investigators were not successful.

[d] Results of this study are also reported in Johnson 2010[37]

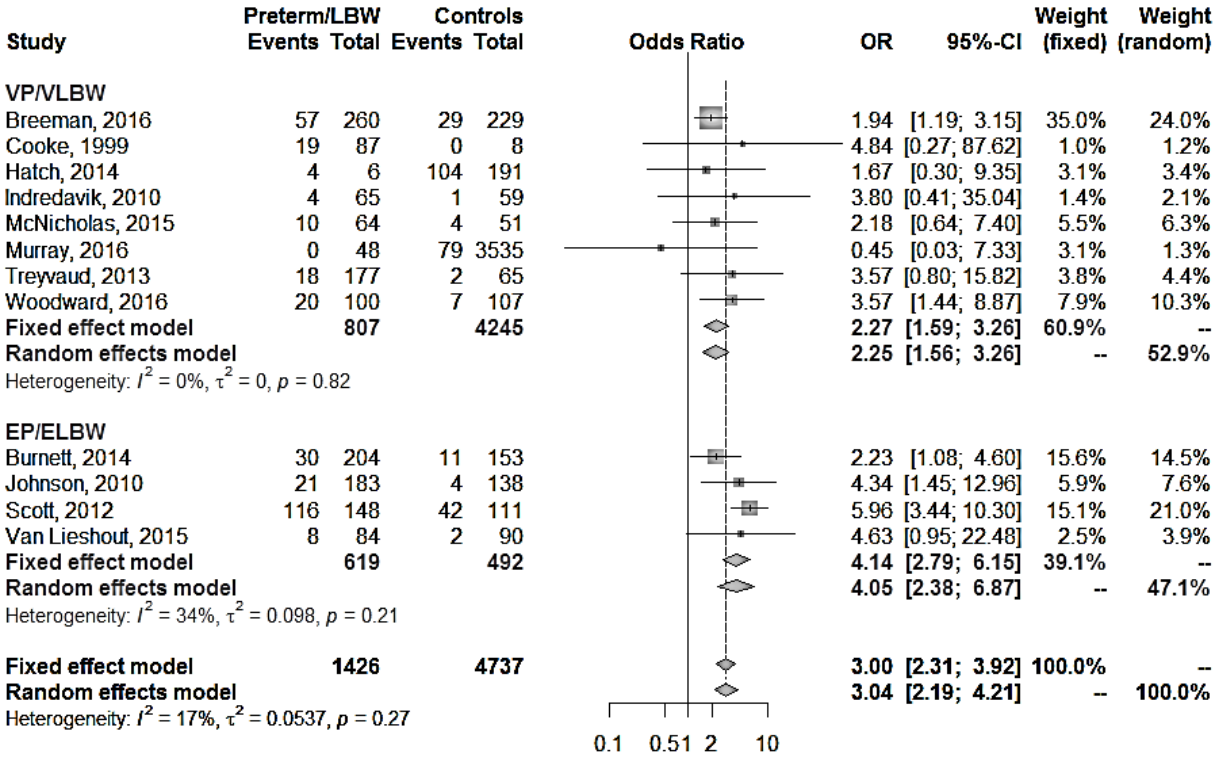


FIGURE 2: Forest plot for ADHD diagnosis categorically defined.

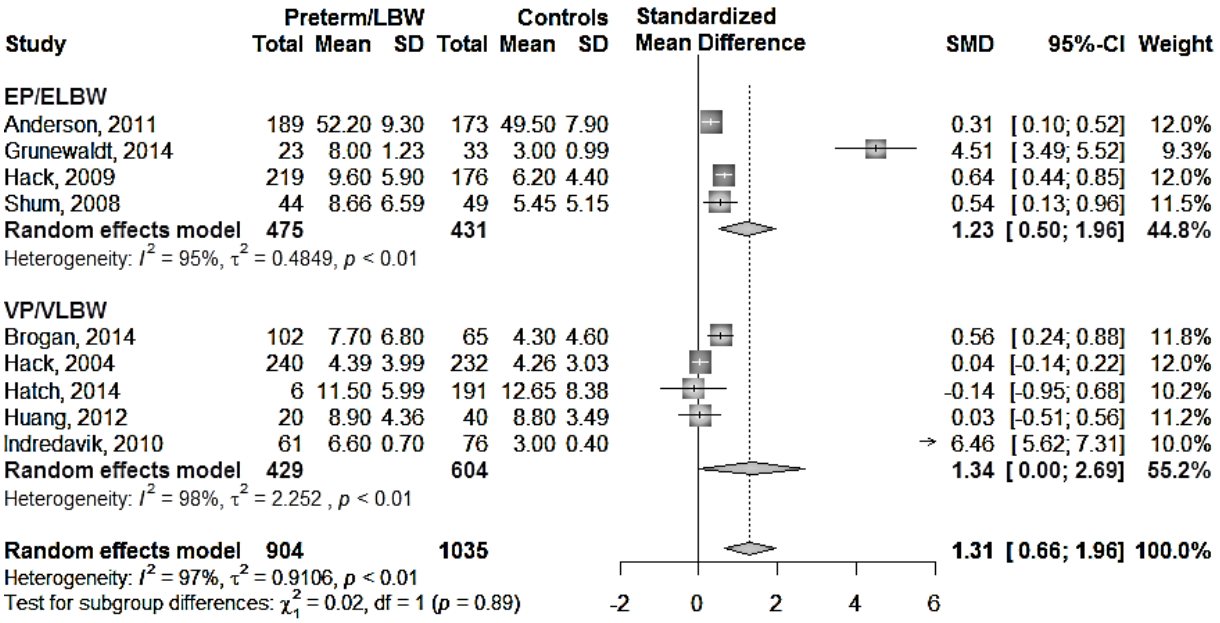


FIGURE 3: Forest plot for ADHD inattentive symptoms.

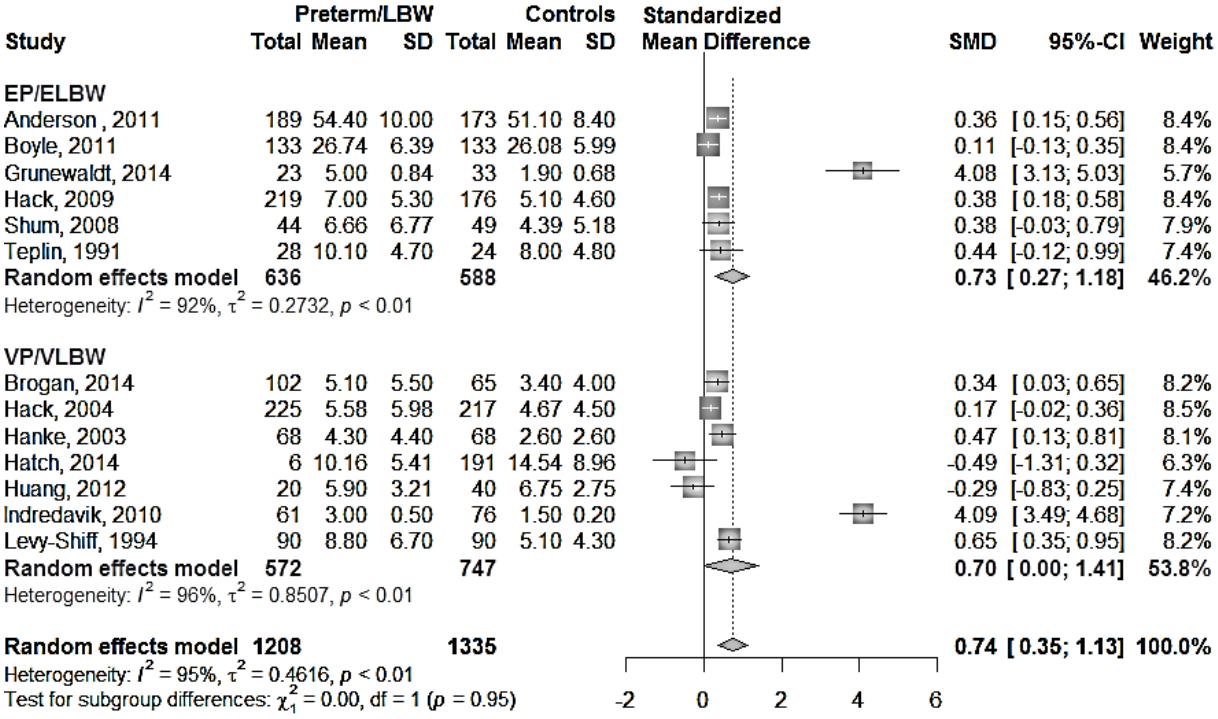


FIGURE 4: Forest plot for ADHD hyperactivity/impulsivity symptoms.

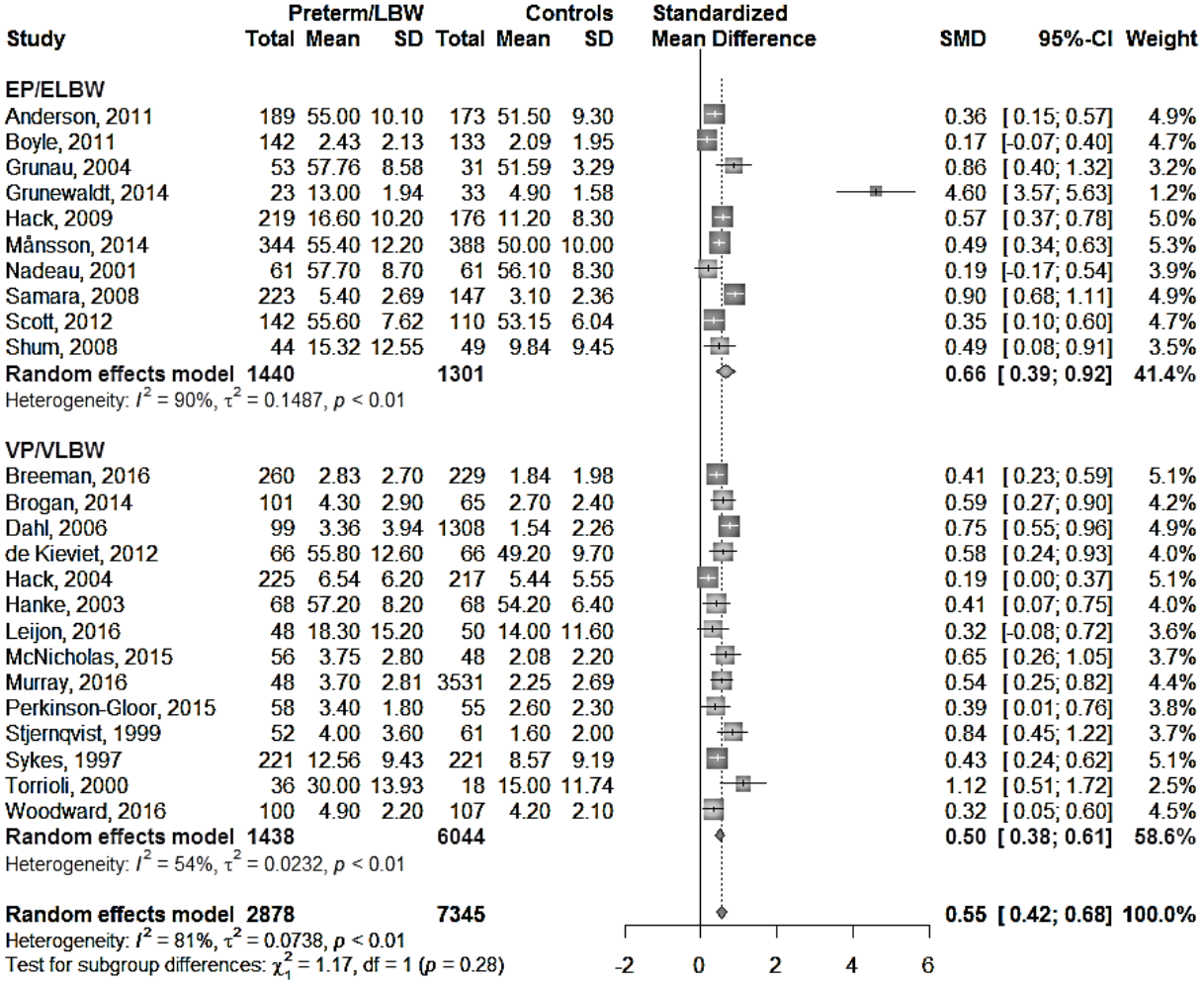


FIGURE 5: Forest plot for ADHD combined symptoms.

Amsterdam Diagnostisch Interview voor Kinderen (ADIKA)
Child and Adolescent Psychiatric Assessment (CAPA)
Cohen-Hoberman Inventory of Physical Symptoms (ChIPS)
Children's Interview for Psychiatric Syndromes-Parent Version (ChIPS-P)
Composite international diagnostic interview (CIDI)
Development and Well-being Assessment (DAWBA)
Diagnostic Interview Schedule for Children (DISC)
Diagnostic Interview for Children and Adolescents (DICA)
Diagnostic Interview Schedule for Children Version IV–Prevalence (DISC-IV-P)
Mannheim Parent Interview (MPI)
Mini-International Neuropsychiatric Interview (MINI)
Schedule for Affective Disorders and Schizophrenia for School-age children ADHD module (K-SADS)

ONLINE APPENDIX FIGURE 1: Diagnostic instruments accepted.

ADHD Rating Scale (ADHD-RS)
Adult ADHD Investigator System Report Scale (AISRS)
Adult ADHD Self-Report Scale (ASRS-v1.1)
Child Behavior Checklist (CBCL)
Child Symptom Inventory-4 (CSI-4)
Conners, Loney, and Milich Scale (CLAM)
Conners' ADHD/DSM-IV scales (CADS)
Conners' parent rating scale (CPRS)
Conners' teacher rating scale (CTRS)
Conners' Abbreviated rating scale (ABRS)
Conners' Abbreviated symptom questionnaire (ASQ)
Conners' Adult ADHD Rating Scales (CAARS)
Conners' Global Index for Parents (CGI-parents)
Conners' Global Index for Teachers (CGI-teacher)
Conners'-Wells Adolescent Self-Report of Symptoms Scale
Disruptive Behavior Rating Scale - Toddler (DBRS - Toddler)
Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBBHKS)
IOWA Conners rating scale - parent
IOWA Conners rating scale - teacher
Parental Account of Children's Symptoms (PACS)
SNAP-IV teacher and parent rating scale.
Swanson, Kotkin, Atkins, MFlynn, Pelham Scale (SKAMP)
Strengths and Difficulties Questionnaire (SDQ)
Strengths and Weaknesses of ADHD Symptoms and Normal Behaviours (SWAN)
Teacher Report Form (TRF)
Teacher Self-control Rating Scale (SCRS)
Teacher Self-control Rating Scale (SCRS)
The ADD/H Comprehensive Teacher Rating Scale (ACTeRS)
Vanderbilt ADHD Teacher Rating Scale (VARTRS)
Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)
Young Adult Self Report (YASR)

ONLINE APPENDIX FIGURE 2: ADHD rating scales accepted**.**

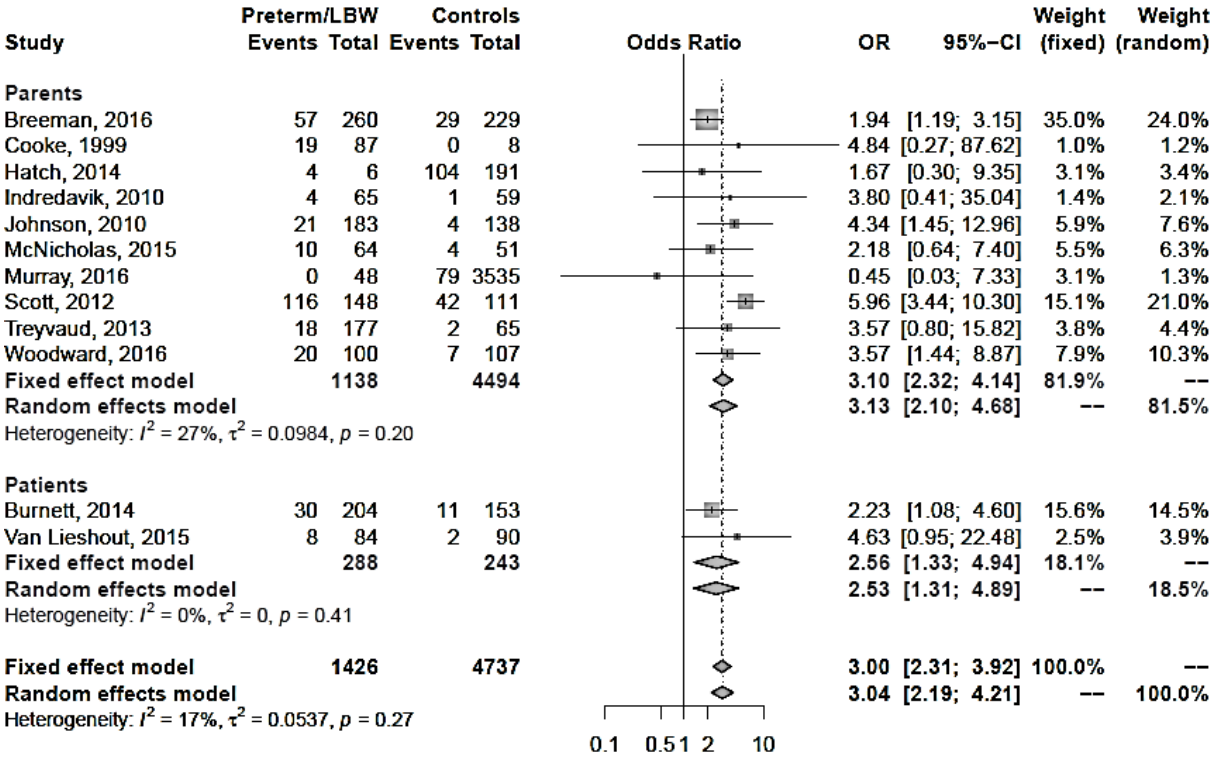
Databases searched:
PubMed/Medline
Lilacs
Cochrane Library
PsycINFO
EMBASE
Centre for Reviews and Dissemination
ClinicalTrials.gov
Current Controlled Trials
National Research Register of Health
Trials Central - online clinical trials listings
Scopus
Web of Science
Main Search strategy used: (Date limit: up to April, 2017)
attention deficit hyperactivity disorder OR ADHD OR hyperactivity disorder OR hyperactivity OR impulsivity OR inattention
(32 weeks OR 32 week) OR (1500g or 1500 g) AND gestat*
Very Low Birth Weight OR VLBW OR Extremely Low Birth Weight OR ELBW OR Extremely Premature Infant OR Premature Birth OR very preterm birth

ONLINE APPENDIX FIGURE 3: Electronic database searched and search terms used.

Newcastle-Ottawa Scale (NOS) - CASE CONTROL					
Selection (OK = 1 stars)				Comparability (OK = 1 or 2 stars)	
1) Definition	2) Representativeness	3) Controls	4) Definition of Controls		Total

Newcastle-Ottawa Scale (NOS) - COHORT					
Selection (OK = 1 stars)				Comparability (OK = 1 or 2 stars)	
1) Representativeness	2) Selection Non-exposed	3) Ascertainment of Exposure	4) Outcome not present		Total

ONLINE APPENDIX FIGURE 4: The Newcastle-Ottawa Scale.



ONLINE APPENDIX FIGURE 5: Forest plot for ADHD categorically defined according to raters.

ONLINE APPENDIX TABLE 1: Sensitivity analysis for categorically defined ADHD.

	VP/VLBW				EP/ELBW				Overall			
	Effect size		Heterogeneity		Effect size		Heterogeneity		Effect size		Heterogeneity	
Study excluded	OR	95%CI	I^2	*P*	OR	95%CI	I^2	*p*	OR	95%CI	I^2	*P*
Breeman 2016[13]	2.76	1.57, 4.86	0%	0.84	-	-	-	-	3.67	2.66, 5.07	0%	0.56
Burnett 2014[43]	-	-	-	-	5.5	3.44, 8.78	0%	0.86	3.2	2.24, 4.63	20%	0.25
Cooke 1999[44]	2.22	1.53, 3.23	0%	0.21	-	-	-	-	3.02	2.13, 4.27	24%	0.21
Hatch 2014[30]	2.28	1.56, 3.33	0%	0.75	-	-	-	-	3.1	2.20, 4.38	22%	0.23
Indredavik 2010[31]	2.22	1.52, 3.23	0%	0.76	-	-	-	-	3.02	2.13, 4.29	25%	0.21
Johnson 2010[37]	-	-	-	-	3.92	1.90, 8.11	56%	0.1	2.94	2.06, 4.21	22%	0.23
McNicholas 2015[32]	2.26	1.53, 3.33	0%	0.73	-	-	-	-	3.11	2.18, 4.44	23%	0.22
Murray 2016[33]	2.32	1.60, 3.36	0%	0.89	-	-	-	-	3.11	2.28, 4.24	13%	0.32
Scott 2012[34]	-	-	-	-	2.92	1.66, 5.14	0%	0.5	2.43	1.79, 3.32	0%	0.85
Treyvaud 2013[42]	2.18	1.49, 3.20	0%	0.78	-	-	-	-	3.01	2.11, 4.30	25%	0.21
Van Lieshout 2015[39]	-	-	-	-	3.94	2.04, 7.59	56%	0.1	2.98	2.10, 4.23	23%	0.22
Woodward 2016[35]	2.05	1.37, 3.08	0%	0.88	-	-	-	-	2.98	2.05, 4.32	24%	0.21

EP/ELBW: Extremely Preterm/Extremely Low Birth Weight; OR: Odds Ratio; VP/VLBW: Very Preterm/Very Low Birth Weight.

ONLINE APPENDIX TABLE 2: Sensitivity analysis for ADHD combined symptoms.

	VP/VLBW				EP/ELBW				Overall			
	Effect size		Heterogeneity		Effect size		Heterogeneity		Effect size		Heterogeneity	
Study excluded	SMD	95% CI	I^2	*p*	SMD	95% CI	I^2	*p*	SMD	95%CI	I^2	*p*
Anderson 2011[48]	-	-	-	-	0.71	0.41, 1.01	91%	<0.01	0.56	0.43, 0.69	81%	<0.01
Boyle 2011[38]	-	-	-	-	0.72	0.44, 1.01	90%	<0.01	0.57	0.44, 0.70	80%	<0.01
Breeman 2016[13]	0.51	0.38, 0.64	57%	<0.01	-	-	-	-	0.56	0.42, 0.69	81%	<0.01
Brogan 2014[49]	0.49	0.37, 0.61	57%	<0.01	-	-	-	-	0.55	0.42, 0.68	81%	<0.01
Dahl 2006[61]	0.46	0.35, 0.57	40%	0.06	-	-	-	-	0.54	0.41, 0.67	80%	<0.01
de Kieviet 2012[50]	0.49	0.37, 0.61	57%	<0.01	-	-	-	-	0.55	0.42, 0.68	81%	<0.01
Grunau 2004[47]	-	-	-	-	0.64	0.36, 0.92	91%	<0.01	0.54	0.41, 0.67	81%	<0.01
Grunewaldt 2014[51]	-	-	-	-	0.48	0.32,0.63	72%	<0.01	0.49	0.40, 0.58	62%	<0.01
Hack 2004[40]	0.53	0.43, 0.63	34%	0.11	-	-	-	-	0.57	0.44, 0.70	80%	<0.01
Hack 2009[41]	-	-	-	-	0.69	0.38, 0.99	91%	<0.01	0.55	0.42, 0.68	81%	<0.01
Hanke 2003[52]	0.51	0.38, 0.63	58%	<0.01	-	-	-	-	0.56	0.42, 0.69	81%	<0.01
Leijon 2016[53]	0.51	0.39, 0.63	57%	<0.01	-	-	-	-	0.56	0.43, 0.69	81%	<0.01
Månsson 2014[45]	-	-	-	-	0.71	0.39, 1.04	91%	<0.01	0.56	0.42, 0.70	81%	<0.01
McNicholas 2015[32]	0.49	0.37, 0.61	56%	<0.01	-	-	-	-	0.55	0.41, 0.68	81%	<0.01
Murray 2016[33]	0.5	0.37, 0.62	57%	<0.01	-	-	-	-	0.55	0.42, 0.68	81%	<0.01
Nadeau 2001[11265917	-	-	-	-	0.71	0.43, 0.99	91%	<0.01	0.56	0.43, 0.69	81%	<0.01

Woodward 2016[35]	0.51	0.39, 0.63	56%	<0.01	-	-	-	-	0.56	0.43, 0.69	81%	<0.01

EP/ELBW: Extremely Preterm/Extremely Low Birth Weight; SMD: Standardized Mean Difference; VP/VLBW: Very Preterm/Very Low Birth Weight.

ONLINE APPENDIX TABLE 3: Sensitivity analysis for ADHD H/I symptoms.

Study excluded	VP/VLBW				EP/ELBW				Overall			
	Effect size		Heterogeneity		Effect size		Heterogeneity		Effect size		Heterogeneity	
	SMD	95%CI	I^2	*p*	SMD	95%CI	I^2	*p*	SMD	95%CI	I^2	*p*
Anderson 2011[48]	-	-	-	-	0.89	0.26, 1.52	94%	<0.01	0.79	0.34, 1.24	95%	<0.01
Boyle 2011[38]	-	-	-	-	0.92	0.34, 1.49	93%	<0.01	0.81	0.37, 1.24	95%	<0.01
Brogan 2014[49]	0.77	-0.10, 1.63	97%	<0.01	-	-	-	-	0.78	0.36, 1.21	95%	<0.01
Grunewaldt 2014[51]	-	-	-	-	0.31	0.19, 0.43	0%	0.45	0.53	0.18, 0.89	94%	<0.01
Hack 2004[40]	0.8	-0.14, 1.74	97%	<0.01	-	-	-	-	0.81	0.36, 1.26	95%	<0.01
Hack 2009[41]	-	-	-	-	0.89	0.25, 1.52	94%	<0.01	0.79	0.34, 1.24	95%	<0.01
Hanke 2003[12655419	0.74	-0.11, 1.60	97%	<0.01	-	-	-	-	0.77	0.35, 1.19	95%	<0.01
Hatch, 2014[30]	0.88	0.12, 1.64	97%	<0.01	-	-	-	-	0.82	0.42, 1.23	95%	<0.01
Huang 2012[60]	0.86	0.09, 1.64	97%	<0.01	-	-	-	-	0.82	0.42, 1.23	95%	<0.01
Indredavik 2010[31]	0.25	-0.01, 0.51	69%	<0.01	-	-	-	-	0.43	0.18, 0.68	86%	<0.01
Levy-Shiff 1994[62]	0.71	-0.16, 1.59	97%	<0.01	-	-	-	-	0.76	0.33, 1.18	95%	<0.01
Shum 2008[56]	-	-	-	-	0.82	0.29, 1.36	94%	<0.01	0.78	0.36, 1.19	95%	<0.01
Teplin 1991[59]	-	-	-	-	0.79	0.28, 1.31	94%	<0.01	0.77	0.36, 1.18	95%	<0.01

EP/ELBW: Extremely Preterm/Extremely Low Birth Weight; SMD: Standardized Mean Difference; VP/VLBW: Very Preterm/Very Low Birth Weight.

ONLINE APPENDIX TABLE 4: Sensitivity analysis for ADHD inattentive symptoms.

	VP/VLBW				EP/ELBW				Overall			
	Effect size		Heterogeneity		Effect size		Heterogeneity		Effect size		Heterogeneity	
Study excluded	SMD	95%CI	I^2	*p*	SMD	95%CI	I^2	*p*	SMD	95%CI	I^2	*P*
Anderson 2011[48]	-	-	-	-	1.75	0.44, 3.06	96%	<0.01	1.48	0.67, 2.29	98%	<0.01
Brogan 2014[49]	1.57	-0.62, 3.76	99%	<0.01	-	-	-	-	1.42	0.68, 2.17	98%	<0.01
Grunewaldt 2014[51]	-	-	-	-	0.49	0.26, 0.73	60%	0.08	0.96	0.35, 1.57	97%	<0.01
Hack 2004[40]	1.71	-0.54, 3.96	98%	<0.01	-	-	-	-	1.51	0.71, 2.31	97%	<0.01
Hack 2009[41]	-	-	-	-	1.65	0.24, 3.07	97%	<0.01	1.43	0.62, 2.24	98%	<0.01
Hatch 2014[30]	1.71	0.14, 3.27	99%	<0.01	-	-	-	-	1.47	0.78, 2.17	98%	<0.01
Huang 2012[60]	1.69	0.01, 3.36	99%	<0.01	-	-	-	-	1.47	0.77, 2.18	98%	<0.01
Indredavik 2010[31]	0.17	-0.15, 0.50	65%	0.03	-	-	-	-	0.63	0.23, 1.03	92%	<0.01
Shum 2008[56]	1.34	0.00, 2.69	98%	<0.01	-	-	-	-	1.42	0.70, 2.14	98%	<0.01

EP/ELBW: Extremely Preterm/Extremely Low Birth Weight; SMD: Standardized Mean Difference; VP/VLBW: Very Preterm/Very Low Birth Weight.

ONLINE APPENDIX TABLE 5: Meta-regression analysis of ADHD rating scales.

Variable	Covariate*		Coefficient	95% CI	*p*
Inattention	Age		0.14	-0.22, 0.51	0.38
	Article quality		1.08	-1.42, 3.60	0.34
	Occurrence of Multiple Births		-0.2	-1.57, 1.17	0.77
	Information Source (Patient)		-1.47	-3.80, 0.85	0.21
	Countries	Norway	5.17	4.11, 6.23	0.0001
		Taiwan	-0.39	-1.53, 0.75	0.5
		UK	0.14	-0.91, 1.19	0.79
		USA	-0.17	-0.97, 0.62	0.66
	ADHD Rating Scale (Inattentive subtype)	ADHD-RS	1.69	-2.29, 5.67	0.4
		Conners	-0.23	-5.35, 4.89	0.92
		CSI-4	0.1	-5.02, 5.22	0.96
		DBRS-Toddler	-0.51	-5.66, 4.63	0.84
Hyperactivity/ Impulsivity	Age		0.01	-0.10, 0.13	0.76
	Article quality		0.31	-0.56, 1.19	0.45
	Occurrence of Multiple Births		0.41	-0.55, 1.38	0.39
	Information Source (Patient)		-0.7	-2.20, 0.80	0.36
	Countries	Canada	-0.25	-0.60, 0.09	0.15
		Germany	0.1	-0.32, 0.53	0.62
		Israel	0.29	-0.10, 0.69	0.14
		Norway	3.72	3.16, 4.28	0.0001
		Taiwan	-0.64	-1.24, -0.05	0.03
		UK	-0.02	-0.42, 0.38	0.92
		USA	-0.1	-0.37, 0.16	0.44
	ADHD Rating Scale (Hyperactivity/impulsivity subtype)	ADHD-RS	0.92	-1.16, 3.01	0.38
		Conners	0.1	-2.11, 2.32	0.92
		CSI-4	0.003	-2.69, 2.70	0.99

		DBRS-Toddler	-0.66	-3.41, 2.08	0.63
		FBBHKS	0.09	-2.62, 2.80	0.94
	Age		-0.007	-0.05, 0.45	0.78
	Article quality		-0.07	-0.34, 0.18	0.55
	Occurrence of Multiple Births		0.06	-0.19, 0.32	0.62
	Information Source (Teacher)		-0.15	-0.75, 0.45	0.62
	Countries	Brazil	0.12	-0.78, 1.02	0.79
		Canada	-0.24	-0.98, 0.49	0.52
		Germany	-0.0085	-0.74, 0.72	0.98
		Ireland	0.1	-0.63, 0.84	0.77
		Italy	0.69	-0.35, 1.74	0.19
		New Zealand	-0.09	-0.99, 0.80	0.83
		Norway	1.28	0.47, 2.08	0.001
Combined		Sweden	0.12	-0.55, 0.80	0.71
		Switzerland	-0.03	0.96, 0.89	0.94
		The Netherlands	0.16	-0.75, 1.08	0.72
		UK	0.33	-0.40, 1.06	0.37
		USA	0.04	-0.59, 0.68	0.88
	ADHD Rating Scale (Combined subtype)	ADHD-RS	4.1	2.91, 5.29	0.6
		CBCL	0.01	-0.51, 0.54	0.95
		Conners	0.03	-0.56, 0.63	0.9
		CSI-4	0.08	-0.54, 0.70	0.8
		SDQ	0.08	-0.45, 0.62	0.75
		TRF	-0.06	-0.68, 0.55	0.83
		YASR	-0.31	-0.88, 0.25	0.27

ADHD-RS: ADHD Rating Scale; CBCL: Child Behavior Checklist; CSI-4: Child Symptom Inventory-4; DBRS-Toddler: Disruptive Behavior Rating Scale - Toddler; FBBHKS: Fremdbeurteilungsbogen für Hyperkinetische Störungen; SDQ: Strengths and Difficulties Questionnaire; TRF: Teacher Report Form; UK: United Kingdom; USA: United States of America; YASR: Young Adult Self Report. *Age, article quality, occurrence of multiple births, and countries were included as continuous variables; Gravidity and Raters were included as categorical variables.

ONLINE APPENDIX TABLE 6: Studies excluded from the meta-analysis, with reasons.

Reference	Reason (s) for Exclusion (s)
Aarnoudse-Moens C, Weisglas-Kuperus N, Duivenvoorden H, Goudoever Jv, Oosterlaan J. 130 Executive Function and it's Impact on Mathematical Underachievement and Attention Problems in Very Preterm Children. *Archives of Disease in Childhood.* 2012;97(Suppl 2):A36-A36.	Conference abstract and/or poster
Aarnoudse-Moens CS, Weisglas-Kuperus N, Duivenvoorden HJ, van Goudoever JB, Oosterlaan J. Executive function and IQ predict mathematical and attention problems in very preterm children. *PloS one.* 2013;8(2):e55994	Not enough information/No answer from the authors
Abernethy LJ, Palaniappan M, Cooke RW. Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight. *Arch Dis Child.* Oct 2002;87(4):279-283.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Astbury J, Orgill A, Bajuk B. Relationship between two-year behaviour and neurodevelopmental outcome at five years of very low-birthweight survivors. *Developmental medicine and child neurology.* Jun 1987;29(3):370-379.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Bohm B, Lundequist A, Smedler AC. Visual-motor and executive functions in children born preterm: the Bender Visual Motor Gestalt Test revisited. *Scandinavian journal of psychology.* Oct 2010;51(5):376-384.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Bora S, Pritchard VE, Chen Z, Inder TE, Woodward LJ. Neonatal cerebral morphometry and later risk of persistent inattention/hyperactivity in children born very preterm. *Journal of child psychology and psychiatry, and allied disciplines.* Jul 2014;55(7):828-838.	Not enough information/No answer from the authors
Botellero VL, Skranes J, Bjuland KJ, et al. Mental health and cerebellar volume during adolescence in very-low-birth-weight infants: a longitudinal study. *Child and adolescent psychiatry and mental health.* 2016;10:6.	Duplicated - same sample as Indredavik 2010[31] (included in the analysis) - University Hospital in Trondheim (1986–1988)
Boulet SL, Schieve LA, Boyle CA. Birth weight and health and developmental outcomes in US children, 1997-2005. *Maternal and child health journal.* Oct 2011;15(7):836-844.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Conrad AL, Richman L, Lindgren S, Nopoulos P. Biological and environmental predictors of behavioral sequelae in children born preterm. *Pediatrics.* Jan 2010;125(1):e83-89.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
D'Onofrio BM, Class QA, Rickert ME, Larsson H, Langstrom N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA psychiatry.* Nov 2013;70(11):1231-1240.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
D'Onofrio B, Class Q, Rickert M, Larsson H, Lanullngstrom N, Lichtenstein P. Psychiatric problems associated with preterm birth: A population-based, quasi-experimental study. *Behaviour Genetics,* 2012; *42*(6):930.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores

Day KL, Van Lieshout RJ, Vaillancourt T, Saigal S, Boyle MH, Schmidt LA. Long-term effects of peer victimization on social outcomes through the fourth decade of life in individuals born at normal or extremely low birthweight. *The British journal of developmental psychology.* Dec 10 2016.	Duplicated - same sample as Boyle 2011[38] and Van Lieshout 2015[39] (both included in the analysis) - Central-west Ontario (1977-1982)
Delobel-Ayoub M, Arnaud C, White-Koning M, et al. Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study. *Pediatrics.* Jun 2009;123(6):1485-1492.	Not enough information/No answer from the authors
Delobel-Ayoub M, Kaminski M, Marret S, et al. Behavioral outcome at 3 years of age in very preterm infants: the EPIPAGE study. *Pediatrics.* Jun 2006;117(6):1996-2005.	Wrong patient population
Elgen SK, Sommerfelt K, Leversen KT, Markestad T. Minor neurodevelopmental impairments are associated with increased occurrence of ADHD symptoms in children born extremely preterm. *European child & adolescent psychiatry.* Apr 2015;24(4):463-470.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Eryigit-Madzwamuse S, Wolke D. Attention problems in relation to gestational age at birth and smallness for gestational age. *Early human development.* Feb 2015;91(2):131-138.	Duplicated - same sample as Breeman 2016[13] (included in the analysis) - The Bavarian Longitudinal Study (1985–1986)
Espirito Santo JL, Portuguez MW, Nunes ML. Cognitive and behavioral status of low birth weight preterm children raised in a developing country at preschool age. *Jornal de pediatria.* Jan-Feb 2009;85(1):35-41.	Wrong patient population
Farooqi A, Hagglof B, Serenius F. Behaviours related to executive functions and learning skills at 11 years of age after extremely preterm birth: a Swedish national prospective follow-up study. *Acta paediatrica.* Jun 2013;102(6):625-634.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Fevang SK, Hysing M, Markestad T, Sommerfelt K. Mental Health in Children Born Extremely Preterm Without Severe Neurodevelopmental Disabilities. *Pediatrics.* Apr 2016;137(4).	Not enough information/No answer from the authors
Ficks CA, Lahey BB, Waldman ID. Does low birth weight share common genetic or environmental risk with childhood disruptive disorders? *Journal of abnormal psychology.* Aug 2013;122(3):842-853.	Wrong patient population
Finnstrom O, Gaddlin PO, Leijon I, Samuelsson S, Wadsby M. Very-low-birth-weight children at school age: academic achievement, behavior and self-esteem and relation to risk factors. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* Aug 2003;14(2):75-84.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores

Fletcher JM, Landry SH, Bohan TP, et al. Effects of intraventricular hemorrhage and hydrocephalus on the long-term neurobehavioral development of preterm very-low-birthweight infants. *Developmental medicine and child neurology.* Sep 1997;39(9):596-606.	Wrong patient population
Foulder-Hughes LA, Cooke RW. Motor, cognitive, and behavioural disorders in children born very preterm. *Developmental medicine and child neurology.* Feb 2003;45(2):97-103.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Gaddlin PO, Finnstrom O, Hellgren K, Leijon I. Hospital readmissions and morbidity in a fifteen-year follow-up of very low birthweight children in Southeast Sweden. *Acta paediatrica.* Apr 2007;96(4):499-505.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Gardner F, Johnson A, Yudkin P, et al. Behavioral and emotional adjustment of teenagers in mainstream school who were born before 29 weeks' gestation. *Pediatrics.* Sep 2004;114(3):676-682.	Not enough information/No answer from the authors
Gücüyener K, Soysal S, Ergenekon E, et al. PO-0399 Neurodevelopmental and Behaviour Outcome of Preterms (ga. *Archives of Disease in Childhood.* 2014;99(Suppl 2):A376-A376.	Conference abstract and/or poster
Gustafsson P, Kallen K. Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: results from a population-based study utilizing the Swedish Medical Birth Register. *Developmental medicine and child neurology.* Mar 2011;53(3):263-268.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Hack M, Breslau N, Aram D, Weissman B, Klein N, Borawski-Clark E. The effect of very low birth weight and social risk on neurocognitive abilities at school age. *Journal of developmental and behavioral pediatrics : JDBP.* Dec 1992;13(6):412-420.	Duplicated - same sample as Hack 2004[40] (included in the analysis) - Rainbow Babies and Children's Hospital (1977–1979)
Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *The New England journal of medicine.* Jul 25 1991;325(4):231-237.	Duplicated - same sample as Hack 2004[40] (included in the analysis) - Rainbow Babies and Children's Hospital (1977–1979)
Hall J, Wolke D. A comparison of prematurity and small for gestational age as risk factors for age 6-13 year emotional problems. *Early human development.* Oct 2012;88(10):797-804.	Duplicated - same sample as Breeman 2016[13] (included in the analysis) - The Bavarian Longitudinal Study (1985–1986)
Hallin AL, Stjernqvist K. Adolescents born extremely preterm: behavioral outcomes and quality of life. *Scandinavian journal of psychology.* Jun 2011;52(3):251-256.	Duplicated - same sample as Stjernqvist 1995[76], (included in the analysis) - University Hospital of Lund, Sweden (1984-1986)
Halmoy A, Klungsoyr K, Skjaerven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. *Biological psychiatry.* Mar 01 2012;71(5):474-481.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores

Healy E. Cognitive, psycho-social, and medical outcomes of very low birth weight infants at age 10-14 years in Ireland. *European Child and Adolescent Psychiatry,* 2013*;22*(2):S142.	Conference abstract and/or poster
Hultman CM, Torrang A, Tuvblad C, Cnattingius S, Larsson JO, Lichtenstein P. Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *Journal of the American Academy of Child and Adolescent Psychiatry.* Mar 2007;46(3):370-377.	Wrong patient population
Indredavik MS, Skranes JS, Vik T, et al. Low-birth-weight adolescents: psychiatric symptoms and cerebral MRI abnormalities. *Pediatric neurology.* Oct 2005;33(4):259-266.	Duplicated - same sample as Indredavik 2010[31] (included in the analysis) - University Hospital in Trondheim (1986–1988)
Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. *Archives of disease in childhood. Fetal and neonatal edition.* Sep 2004;89(5):F445-450.	Duplicated - same sample as Indredavik 2010[31] (included in the analysis) - University Hospital in Trondheim (1986–1988)
Jaekel J, Wolke D, Bartmann P. Poor attention rather than hyperactivity/impulsivity predicts academic achievement in very preterm and full-term adolescents. *Psychological medicine.* Jan 2013;43(1):183-196.	Duplicated - same sample as Breeman 2016[13], (included in the analysis) - The Bavarian Longitudinal Study (1985–1986)
Johnson KA, Healy E, Dooley B, Kelly SP, McNicholas F. Children born with very low birth weight show difficulties with sustained attention but not response inhibition. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence.* 2015;21(5):629-647.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Johnson S, Kochhar P, Hennessy E, Marlow N, Wolke D, Hollis C. Antecedents of Attention-Deficit/Hyperactivity Disorder Symptoms in Children Born Extremely Preterm. *Journal of developmental and behavioral pediatrics : JDBP.* May 2016;37(4):285-297.	Duplicated - same sample as Johnson 2010[37] (included in the analysis) -EPICure Study (March - December 1995)
Kittler PM, Gardner JM, Lennon EM, Flory MJ, Mayes LC, Karmel BZ. The development of selective attention and inhibition in NICU graduates during the preschool years. *Developmental neuropsychology.* 2011;36(8):1003-1017.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Klebanov PK, Brooks-Gunn J, McCormick MC. Classroom behavior of very low birth weight elementary school children. *Pediatrics.* Nov 1994;94(5):700-708.	Not enough information/No answer from the authors
Krageloh-Mann I, Toft P, Lunding J, Andresen J, Pryds O, Lou HC. Brain lesions in preterms: origin, consequences and compensation. *Acta paediatrica.* Aug 1999;88(8):897-908.	Not enough information/No answer from the authors
Lahat A, Van Lieshout RJ, Saigal S, Boyle MH, Schmidt LA. ADHD among young adults born at extremely low birth weight: the role of fluid intelligence in childhood. *Frontiers in psychology.* 2014;5:446.	Duplicated - same sample as Boyle 2011[38] and Van Lieshout 2015[39] (both included in the analysis) - Central-west Ontario (1977-1982)

Langerock N, van Hanswijck de Jonge L, Bickle Graz M, Huppi PS, Borradori Tolsa C, Barisnikov K. Emotional reactivity at 12 months in very preterm infants born at <29 weeks of gestation. *Infant behavior & development.* Jun 2013;36(3):289-297.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Lean RE. The Attention Abilities and Grey Matter Development of School Aged Children Born Very Preterm. *Arts & Sciences Electronic Theses and Dissertations*. 2015;660.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Lindström K, Lindblad F, Hjern A. Preterm birth and ADHD in schoolchildren - A Swedish national cohort study. *Acta Paediatrica, International Journal of Paediatrics,* 2010; *99*: 66	Duplicated - same sample as Lindström 2009[77] (included in the analysis) - Swedish national registers (1973-1979)
Lindstrom K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics.* Jan 2009;123(1):e47-53.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Lindstrom K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. *Pediatrics.* May 2011;127(5):858-865.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Loe IM, Lee ES, Luna B, Feldman HM. Behavior problems of 9-16 year old preterm children: biological, sociodemographic, and intellectual contributions. *Early human development.* Apr 2011;87(4):247-252.	Wrong patient population
Lowe J, MacLean PC, Shaffer ML, Watterberg K. Early working memory in children born with extremely low birth weight: assessed by object permanence. *Journal of child neurology.* Apr 2009;24(4):410-415.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Lozano-Botellero V, Indredavik M, Skranes J, Lydersen S, Brubakk A, Martinussen M. PO-0005 Cerebellum, Thalamus and Cerebral Cortex in Vlbw Adolescents' Mental Health. *Archives of Disease in Childhood.* 2014;99(Suppl 2):A253-A253.	Conference abstract and/or poster
Lozano-Botellero V, Indredavik M, Skranes J, Lydersen S, Brubakk A, Martinussen M. PO-0004 Entorhinal Cortical Thinning and ADHD And Relational Problems in VLBW Adolescents. *Archives of Disease in Childhood.* 2014;99(Suppl 2):A252-A253.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Lund LK, Vik T, Skranes J, Brubakk AM, Indredavik MS. Psychiatric morbidity in two low birth weight groups assessed by diagnostic interview in young adulthood. *Acta paediatrica.* Apr 2011;100(4):598-604.	Duplicated - same sample as Indredavik 2010[31] (included in the analysis) - University Hospital in Trondheim (1986–1988)
McCormick MC, Gortmaker SL, Sobol AM. Very low birth weight children: behavior problems and school difficulty in a national sample. *The Journal of pediatrics.* Nov 1990;117(5):687-693.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores

Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV. Impact of low birth weight on attention-deficit hyperactivity disorder. *Journal of developmental and behavioral pediatrics : JDBP.* Feb 2002;23(1):16-22.	Wrong patient population
Modrusan-Mozetic Z, Prpic I, Sindicic-Simundic N, Cicvaric-Vlasic I, Paucic-Kirincic E. Neurological and cognitive outcome of extremely low birth weight (ELBW) and very low birth weight (VLBW) infants and two at four years of age. *Paediatria Croatica.* 2003;*47*(2):57-60.	Abstract only
Morales MR, Polizzi C, Sulliotti G, Mascolino C, Perricone G. Early Precursors of Low Attention and Hyperactivity in Moderately and Very Preterm Children at Preschool Age. Pediatric Reports. 2013;5(4):e18.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Morsing E, Asard M, Ley D, Stjernqvist K, Marsal K. Cognitive function after intrauterine growth restriction and very preterm birth. *Pediatrics.* Apr 2011;127(4):e874-882.	Not enough information/No answer from the authors
Mulder H, Pitchford NJ, Marlow N. Inattentive behaviour is associated with poor working memory and slow processing speed in very preterm children in middle childhood. *The British journal of educational psychology.* Mar 2011;81(Pt 1):147-160.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Mulder H, Pitchford NJ, Marlow N. Processing speed mediates executive function difficulties in very preterm children in middle childhood. *Journal of the International Neuropsychological Society : JINS.* May 2011;17(3):445-454.	Duplicated - same sample as Samara 2008[36] (included in the analysis) - EPICure Study (March - December 1995)
Murray AL, Scratch SE, Thompson DK, et al. Neonatal brain pathology predicts adverse attention and processing speed outcomes in very preterm and/or very low birth weight children. Neuropsychology. Jul 2014;28(4):552-562.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Murray E, Matijasevich A, Santos IS, et al. Sex differences in the association between foetal growth and child attention at age four: specific vulnerability of girls. *Journal of child psychology and psychiatry, and allied disciplines.* Dec 2015;56(12):1380-1388.	Duplicated - Same sample as Murray 2016[33] (included in the analysis) - 2004 Pelotas Cohort
Nigg JT, Breslau N. Prenatal smoking exposure, low birth weight, and disruptive behavior disorders. *Journal of the American Academy of Child and Adolescent Psychiatry.* Mar 2007;46(3):362-369.	Wrong patient population
O'Callaghan MJ, Burns YR, Gray PH, et al. School performance of ELBW children: a controlled study. *Developmental medicine and child neurology.* Oct 1996;38(10):917-926.	Not enough information/No answer from the authors
O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. *Pediatrics.* Aug 2003;112(2):301-307.	Wrong patient population

Pettersson E, Sjolander A, Almqvist C, et al. Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. *Journal of child psychology and psychiatry, and allied disciplines.* Apr 2015;56(4):453-459.	Wrong patient population
Pizzo R, Urben S, M VDL, et al. Attentional networks efficiency in preterm children. *Journal of the International Neuropsychological Society : JINS.* Jan 2010;16(1):130-137.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Poole KL, Schmidt LA, Missiuna C, Saigal S, Boyle MH, Van Lieshout RJ. Childhood motor coordination and adult psychopathology in extremely low birth weight survivors. *Journal of affective disorders.* Jan 15 2016;190:294-299.	Duplicated - same sample as Boyle 2011[38] and Van Lieshout 2015[39] (both (included in the analysis) - Central-west Ontario (1977-1982)
Potgieter S, Vervisch J, Lagae L. Event related potentials during attention tasks in VLBW children with and without attention deficit disorder. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* Oct 2003;114(10):1841-1849.	Wrong patient population
Potgieter ST, de Cock P. Information processing in very-low-birth-weight children with and without attention deficit disorder. *Biology of the neonate.* 2004;85(3):203-209.	Wrong patient population
Rommel AS, James SN, McLoughlin G, et al. Association of Preterm Birth with Attention-Deficit/Hyperactivity Disorder-Like and Wider-Ranging Neurophysiological Impairments of Attention and Inhibition. *Journal of the American Academy of Child and Adolescent Psychiatry.* Jan 2017;56(1):40-50.	Wrong patient population
Saigal S, Pinelli J, Hoult L, Kim MM, Boyle M. Psychopathology and social competencies of adolescents who were extremely low birth weight. *Pediatrics.* May 2003;111(5 Pt 1):969-975.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Saigal S, Stoskopf BL, Streiner DL, Burrows E. Physical growth and current health status of infants who were of extremely low birth weight and controls at adolescence. *Pediatrics.* Aug 2001;108(2):407-415.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Shamberger R. Attention-deficit disorder associated with breast-feeding: a brief report. Journal of the American College of Nutrition. Aug 2012;31(4):239-242.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics.* Jan 2014;133(1):e14-22.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Simic N, Asztalos EV, Rovet J. Impact of neonatal thyroid hormone insufficiency and medical morbidity on infant neurodevelopment and attention following preterm birth. *Thyroid : official journal of the American Thyroid Association.* Apr 2009;19(4):395-401.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores

Singh GK, Kenney MK, Ghandour RM, Kogan MD, Lu MC. Mental Health Outcomes in US Children and Adolescents Born Prematurely or with Low Birthweight. *Depression research and treatment.* 2013;2013:570743.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Skranes J, Vangberg TR, Kulseng S, et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain : a journal of neurology.* Mar 2007;130(Pt 3):654-666.	Duplicated - same sample as Indredavik 2010[31] (included in the analysis) - University Hospital in Trondheim (1986–1988)
Stein RE, Siegel MJ, Bauman LJ. Are children of moderately low birth weight at increased risk for poor health? A new look at an old question. *Pediatrics.* Jul 2006;118(1):217-223.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Stjernqvist K, Svenningsen NW. Extremely low-birth-weight infants less than 901 g: development and behaviour after 4 years of life. *Acta paediatrica.* May 1995;84(5):500-506.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Strang-Karlsson S, Raikkonen K, Pesonen AK, et al. Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. *The American journal of psychiatry.* Oct 2008;165(10):1345-1353.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores
Szatmari P, Saigal S, Rosenbaum P, Campbell D, King S. Psychiatric disorders at five years among children with birth weights less than 1000 g: a regional perspective. *Developmental medicine and child neurology.* Nov 1990;32(11):954-962.	Duplicated - same sample as Boyle 2011[38] and Van Lieshout 2015[39] (both included in the analysis) - Central-west Ontario (1977-1982)
Taylor HG, Margevicius S, Schluchter M, Andreias L, Hack M. Persisting behavior problems in extremely low birth weight adolescents. *Journal of developmental and behavioral pediatrics : JDBP.* Apr 2015;36(3):178-187.	Duplicated - same sample as Hack 2009[41] (included in the analysis) - Rainbow Babies and Children's Hospital (1992–1995)
Tsekoura E, Sdona E, Kotsia E, Orfanidou I, Matziota A, Alexopoulou E. The epidemic of multiple births: Data from a tertiary center follow up program of high risk neonates. *Journal of Maternal-Fetal and Neonatal Medicine.* 2014;*27*: 424.	Conference abstract and/or poster
Ure A, Doyle LW, Northam E, Treyvaud K, Anderson,P J. The clinical presentation of ADHD and ASD symptoms in children born preterm. *J Paediatr Child Health.* 2012;*48*: 109.	Conference abstract and/or poster
van der Meere J, Borger NA, Potgieter ST, Pirila S, De Cock P. Very low birth weight and attention deficit/hyperactivity disorder. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence.* Nov 2009;15(6):605-618.	Wrong patient population
Van Hus JW, Potharst ES, Jeukens-Visser M, Kok JH, Van Wassenaer-Leemhuis AG. Motor impairment in very preterm-born children: links with other developmental deficits at 5 years of age. *Developmental medicine and child neurology.* Jun 2014;56(6):587-594.	Not enough information/No answer from the authors

Verkerk G, Houtzager B, JeukensVisser M, et al 325 Attention Problems in Very Low Birth Weight Preschoolers. *Archives of Disease in Childhood*. 2012;97:A95.	Duplicated - same sample as Van Hus 2014 - Emma's Children's Hospital/Academic medical Centre, Amsterdam (2007-2009)
Wall BM.Executive function of children born preterm. *ProQuest Information & Learning, US.* 1996; 57.	Wrong patient population
Whitaker AH, Van Rossem R, Feldman JF, et al. Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. *Archives of general psychiatry.* Sep 1997;54(9):847-856.	Wrong patient population
Wilson-Ching M, Molloy CS, Anderson VA, et al. Attention difficulties in a contemporary geographic cohort of adolescents born extremely preterm/extremely low birth weight. Journal of the International Neuropsychological Society : JINS. Nov 2013;19(10):1097-1108.	Duplicated - same sample as Burnett 2014[43] (included in the analysis) - Victorian Infant Collaborative Study Group (1991-1992)
Woodward LJ, Bora S, Moor S. Psychiatric outcomes at age 9 of a regional cohort of children born very preterm. *J Paediatr Child Health,* 2012;*48*:39.	Conference abstract and/or poster
Yau G, Schluchter M, Taylor HG, et al. Bullying of extremely low birth weight children: associated risk factors during adolescence. *Early human development.* May 2013;89(5):333-338.	Duplicated - same sample as Hack 2009[41] (included in the analysis) - Rainbow Babies and Children's Hospital (1992–1995)
Ziborova M, Keshishian E, Sakharova E, Burdukova J. Delayed neurodevelopmental outcomes in pre-/early school-aged VPT/VLBW children. *Journal of Maternal-Fetal and Neonatal Medicine.* 2014;*27*: 263.	Measure not assessing/deriving strictly DSM/ICD ADHD diagnosis or dimensional scores

7.2 ARTIGO 2

Título: Predicting Attention-Deficit/Hyperactivity Disorder in Very Preterm/Very Low Birth Weight Newborns

Status: Pronto para ser submetido.

Carta de submissão:

Confirmação de submissão:

Versão do manuscrito submetida:

Predicting Attention-Deficit/Hyperactivity Disorder in Very Preterm/Very Low Birth Weight Newborns

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Abstract

Objective: To develop a predictive score and individualized risk calculator for attention-deficit/hyperactivity disorder (ADHD) in very preterm/very low birth weight (VP/VLBW) newborns.

Methods: We collected 31 gestational and neonatal data in a clinical cohort of 104 VP/VLBW newborns delivered at a Brazilian tertiary care hospital from 2010 to 2012. Children were assessed at 6 years of age for ADHD, confirmed through clinical interviews using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). The least absolute shrinkage and selection operator (LASSO) method was used for model-building.

Results: A total of 96 VP/VLBW children were assessed at 6 years of age (92.3% follow-up), of whom 32 (33.3%) were diagnosed with ADHD. The area under the curve (AUC) for predicting ADHD based on seven parameters (late-onset sepsis confirmed by blood culture, necrotizing enterocolitis, neonatal seizures, periventricular leukomalacia, respiratory distress syndrome, length of hospital stay and number of maternal ADHD symptoms) was 0.875 (CI, 0.800–0.942, $p<0.001$; AUC corrected for optimism with bootstrapping: 0.806). The model showed specificity for ADHD compared to other common child psychopathology (anxiety and oppositional defiant disorders). The risk calculator, available at https://jscalc.io/source/unaQG5TuvzVzuzmV, proved useful to guide intervention within a 31–62% range of ADHD risk.

Conclusions: The risk calculator showed good performance parameters and is a potential practical clinical tool for early identification of VP/VLBW children at high risk of future ADHD diagnosis. Replication in further studies is needed to establish external validity in population-based samples and confirm clinical usefulness.

INTRODUCTION

Preterm birth and low birth weight remain at high incidence levels worldwide (1). In 2014, 14.84 million newborns, an estimated 10.4% of all babies born globally that year, were born preterm (before 37 completed weeks of gestation) (1). In 2015, 14.6% of all babies were born with low birth weight (2). accounting for 20.5 million babies being born with less than 2,500g (2). Together, preterm birth and low birth weight accounted for about 17% of infant deaths in 2016 in the U.S. alone (3). Besides this high mortality rate, survivors can face lifelong morbidity, including motor, sensorial, cognitive, and psychiatric disorders (4), especially at higher degrees of prematurity and low birth weight. Very preterm (VP) – those born at gestational age less than 32 weeks (5), who represent 15.6% of all preterm newborns (6) – and those with very low birth weight (VLBW) – weighing less than 1,500 grams (5), corresponding to 1.42% of all U.S. births in 2015 (7) – are particularly vulnerable to these adverse outcomes (8, 9).

Attention-deficit/hyperactivity disorder (ADHD) is defined as a non-episodic, excessive, and impairing pattern of inattention and/or hyperactivity/impulsivity (10). Its worldwide prevalence is estimated at 3.4% (11) to 5.3% (12) in children and adolescents. Among all environmental risk factors for ADHD, VP/VLBW are the most consistent ones (13). A previous systematic review and meta-analysis (14) found that children or adolescents born VP/VLBW are about three times more likely to be diagnosed with ADHD than full-term babies. The reasons for increased vulnerability to ADHD in VP/VLBW individuals remain unknown, but a number of hypotheses have been put forward, including higher frequency of pre- and post-natal adversities, parental and biological issues such as hypothalamic–pituitary–adrenal axis dysregulations, and perinatal systemic inflammation, which could cause structural and functional brain disorders (such as ADHD) and other psychiatric and developmental disorders (15-19). In addition, several maternal and neonatal characteristics and morbidities associated with preterm birth and low birth weight (such as low socioeconomic status, male sex, necrotizing enterocolitis, peri- and intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, neonatal chronic lung disease, low Apgar scores after birth, white matter injury, slow head

growth, among others(15)) may be linked to the etiology of ADHD. However, it remains unclear how these factors might combine to influence the development of ADHD.

To date, clinicians have no clue to discriminate which among those children born VP/VLBW will actually develop ADHD in the future, based only on the clinical presentation at birth. Considering the high prevalence of ADHD and its negative consequences for individuals and society (20, 21), a better understanding of risk factors for this condition may lead to strategies for specific neonatology, pediatric, and psychiatric prevention and early interventions to minimize the ADHD burden.

A systematic review by Bernardini et al. (2017) (22) showed the feasibility of developing risk prediction models for assessing how to combine factors that can influence the risk of developing psychiatric disorders. However, to date, no study has quantified the weight that each perinatal risk factor has on later development of ADHD in VP/VLBW newborns, and there are no instruments available to predict their risk of developing ADHD.

In this context, the aim of this study is to develop a multivariable predictive model and to build a practical online individualized risk calculator to help clinicians identify, among VP/VLBW newborns, those who are most likely to have ADHD in the future, using predictors that are easily collected in the Neonatal Intensive Care Unit (NICU) setting. Our hypothesis is that this early screening tool based on risk factors related to preterm birth/low birth weight will have an acceptable prognostic performance for ADHD in VP/VLBW newborns.

METHODS

The methods followed recommendations offered by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement (23). This study was preregistered at *Plataforma Brasil* (number: 46376115.1.0000.5327) and was approved by the local institutional review board (number: 15-0384). Mothers provided written consent to participate in the study. A summary of key study characteristics can be found in Supplementary Table 1.

Source of Data

To develop the predictive model and the risk calculator, we used data from a prospective outpatient follow-up program of VP/VLBW babies who were born at *Hospital de Clínicas de Porto Alegre* (HCPA), a university-affiliated tertiary care hospital in the southernmost state of Brazil.

Participants

We selected all VP/VLBW children (gestational age less than 32 weeks and/or birth weight less than 1,500 g (5)) born at HCPA between January 1st, 2010 and December 31st, 2012. All families of children born during this period were contacted and invited to enter the study. Children from families who agreed to participate were assessed between October 2015 and September 2017, when they were around the age of 6. We excluded newborns whose mothers were HIV-positive, as well as newborns with genetic syndromes, congenital infection, or cerebral palsy.

Outcomes

The main outcome was the categorical diagnosis of ADHD, confirmed through clinical interviews with the mother when the child was around 6 years old. A trained child and adolescent psychiatrist (APF) used a validated Brazilian version (24) of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL) (25), a semi-structured interview based on DSM-IV criteria widely used for psychiatric diagnose. To test specificity in predicting ADHD, we also tested how the model predicted two common disorders in this population: anxiety disorders and oppositional defiant disorder, also assessed by K-SADS-PL.

Predictors

During the hospital stay, a trained neonatology student collected maternal and neonatal data from medical records. All potential predictors of ADHD (based on previous literature review and availability) were selected a priori. This included the following variables (definitions in Supplementary Table 2):

Categorical gestational variables: chronic arterial hypertension during pregnancy; gestational diabetes mellitus; low socioeconomic status; pre-eclampsia; prolonged rupture of membranes; syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpesvirus (STORCH) infection; and urinary tract/ovarian infection.

Categorical neonatal variables: bronchopulmonary dysplasia; chorioamnionitis; delayed birth weight recovery; hypoglycemia; late-onset sepsis confirmed by blood culture; male sex; mechanical ventilation**;** necrotizing enterocolitis; neonatal seizures; peri- or intraventricular hemorrhage (grade 2, 3, or 4); periventricular leukomalacia**;** respiratory distress syndrome; retinopathy of prematurity; small for gestational age status; and transient tachypnea of the newborn.

Continuous variables: Apgar score at 1 and 5 minutes after birth, birth weight, gestational age, head circumference at discharge (z scores), length of hospital stay, Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II), total parenteral nutrition time in days, and maternal ADHD symptoms assessed by means of the Adult ADHD Self-Report Scale (ASRS-18). The latter has proven effectiveness in adult ADHD screening, with high sensitivity and moderate specificity (26), and has been cross-culturally adapted into Brazilian Portuguese (27). The ASRS-18 was the only predictor that was not collected at perinatal time, but at the same time as the child was evaluated for ADHD, around the age of 6. It consists of items inquiring about the frequency of all 18 DSM-IV Criterion A symptoms of adult ADHD. Each of these items is assigned a score (0 to 4) based on the frequency of the symptoms.

Missing data

To minimize the bias of excluding newborns with unavailable predictors or outcomes, we used a multiple imputation model (10 imputations) run in the MICE package (28) of R software (29). For all missing data, including predictors and

outcomes, we used the predictor matrix. Binary predictors were handled by logistic regression, and continuous data by predictive mean matching. No iterations were included in the imputation model.

Statistical analysis methods

All statistical analyses were computed using the R software version 3.5.2 (29).

For the model-building procedure, the least absolute shrinkage and selection operator (LASSO) technique was used for variable selection and regularization. This technique is a penalized regression method that does not require univariate analysis to select variables. It is recommended for use when there is a small sample size and many potential predictors, minimizing model overfitting when there are few events relative to the number of predictors (30). LASSO was implemented with the GLMNET package (31). The penalization factor (lambda) was selected with a 10-fold cross-validation procedure (Supplementary Figure 1), which reduces bias and variability of the performance estimates.

The following model performance measures were used to assess the predicted probabilities obtained by these analyses: overall performance, calculated by the R^2 statistic; discrimination, calculated by the area under the receiver operating characteristic curve (ROC); internal validation with bootstrap inference, assessed using 1000 replications; calibration, assessed by plotting observed vs. predicted probabilities; prediction density plots and accuracy, assessed across a range of probability thresholds. We additionally explored the potential clinical usefulness of the risk calculator using Net Benefit analyses (32, 33).

RESULTS

Participants

Overall, 208 VP/VLBW newborns were born at HCPA between 2010 and 2012; of these, 129 survived (62%). After application of the exclusion criteria, 104 children

were eligible for evaluation and entered the analyses. Ninety-six (92.3%) were assessed for ADHD at a mean age of 5.53 years (range: 4.33–7.54), and eight children were not located. A total of 32 children (33.3%) were reported to have a categorical diagnosis of ADHD. A full flow diagram of participant selection can be found in Figure 1. The frequency of continuous and categorical maternal and neonatal variables, as well as the categorical outcomes, is summarized in Table 1.

Model development

The 10-fold cross-validation analyses performed by LASSO selected a penalization factor (lambda) of 0.07242856 (Supplementary Figure 2). Among all 31 potential predictors, this lambda selected the following seven final variables for the predicting model: late-onset sepsis confirmed by blood culture, necrotizing enterocolitis, neonatal seizures, periventricular leukomalacia, respiratory distress syndrome, length of hospital stay, and maternal ASRS-18 score.

Model specification

Table 2 presents the specifications of the predictive model, with the selected variables, respective regression coefficients, and model intercept to allow predictions for individuals. Table 2 also shows the risk score formula and the site where the individualized ADHD risk calculator can be found (https://jscalc.io/calc/unaQG5TuvzVzuzmV).

Model performance

The selected variables explained a proportion of 34.9% (R^2) of the variance in ADHD diagnosis. The predictive model discriminated between ADHD vs. no ADHD at follow-up with an AUC of 0.875 (confidence interval (CI) 0.80–0.942, $p<0.001$) (Figure 2). Correction for optimism with bootstrapping yielded an AUC of 0.806. The bias-corrected calibration plot showed that predicted probability and observed frequency of

ADHD moderately agreed throughout the range of risk (Figure 3). Supplementary Figure 3 shows the frequency of individuals over a range of risk estimates. The range of estimated risk went from a minimum of 14.58% to a maximum of 82.93%. Supplementary Figure 4 (prediction density plot) shows the distribution of negative and positive cases across a range of probability thresholds. Supplementary Figure 5 shows the accuracy across the range of probability thresholds. The best accuracy (86%) is achieved when a positive class is thresholded at 30%. As shown in Figure 4, use of the model was associated with significant net benefits. The estimated decision curve shows that, compared with “no intervention”, using the risk calculator is associated with net benefits for probabilities ranging from 0% to 62% risk of developing ADHD. Compared to an “intervention to all” approach, the risk calculator is as useful at the ranges of 0% to 31% and is statistically more useful at the ranges above 31%.

Model specificity

As shown in Supplementary Figure 6 and 7, the performances of model discrimination predicting any anxiety disorder and oppositional defiant disorder were significantly lower than for ADHD (AUC for anxiety disorder: 0.507; AUC for oppositional defiant disorder: 0.540).

DISCUSSION

Using a well-defined clinical diagnosis of ADHD in a birth-cohort with a high follow-up rate, we constructed an online individualized risk calculator to predict, which VP/VLBW newborns will be diagnosed with ADHD around 6 years later. We found that the combination of total number of the maternal ADHD symptoms and some neonatal categorical data (length of hospital stay, late-onset sepsis confirmed by blood culture, necrotizing enterocolitis, neonatal seizures, periventricular leukomalacia, and respiratory distress syndrome) achieved good performance to discriminate between those who will develop ADHD vs. those who will not. The model showed specificity for

ADHD compared to other common child psychopathology (anxiety disorders and oppositional defiant disorder).

Our risk calculator was able to discriminate those newborns with the highest risk for ADHD. We achieved good discriminatory performance for distinguishing between ADHD and non-ADHD individuals (AUC: 0.806). Furthermore, a predicted ADHD risk of 30% provided the best balance between sensitivity and specificity within the generating sample. Using a decision curve analysis approach to investigate the clinical usefulness of the risk calculator in VP/VLBW newborns, we found that offering interventions to high ADHD risk individuals would be associated with statistically significant net benefits, at a range of ADHD risk from 31% to 62%. This means that a VP/VLBW individual would unlikely need a clinical assessment to receive indicated interventions when his or her 6-year risk of ADHD is lower or greater than this range, which is a relevant clinical information.

It is important to highlight that the variables selected by the predictive model have biological plausibility to explain the occurrence of ADHD. This disorder is known to have a multifactorial etiology, with a high heritability (around 75%) shown in family, twin, and adoption studies (34). The risk calculator captures this genetic component by including the total number of maternal ADHD symptoms from the ASRS-18. However, as VP/VLBW newborns are approximately three times more likely than full-term infants to develop ADHD (14), gestational and perinatal characteristics may also have a role in this increased frequency (35). Neonatal seizures and periventricular leukomalacia could be related to impaired neural development in these newborns. However, not only local brain damage may be involved; other neonatal morbidities associated with preterm birth as respiratory distress syndrome, late-onset sepsis, necrotizing enterocolitis, producing a pro-inflammatory response via cytokines that promote activation of microglia (36). resulting in an inflammatory flow that further contributes to neuroinflammation (37, 38) and, theoretically, to the pathophysiology of ADHD (39, 40).

The performance achieved by our risk calculator was similar to that of others developed to predict other psychiatric disorders (41). However, we are not aware of previous attempts to create a risk calculator to predict ADHD diagnosis in VP/VLBW

newborns. A study by Scwenke et al. (2018) (42) also used pregnancy and birth characteristics to predict ADHD in a hospital-based birth cohort, but did not focus on VP/VLBW. In this study, only smoking (OR: 2.63; 95% CI, 1.39–4.97) and 1-minute Apgar score (OR: 0.76; 95% CI, 0.61–0.94) were predictors of ADHD in the multivariable logistic regression model. No significant associations with later development of ADHD were found for Apgar scores at 5 and 10 minutes after birth, mode of delivery, maternal educational level, number of pregnancies, breastfeeding, alcohol use during pregnancy, age at labor, birth weight, umbilical artery pH, or duration of pregnancy. However, the rate of follow-up was only 15.4%, and several potential risk factors and outcomes were collected retrospectively based on questionnaires sent to mothers. For ADHD, for example, the mother was only asked whether her child was known to have a diagnosis of ADHD and whether the child was taking medication for the condition. No risk calculator was developed in this study. In another study, Caye et al. (2019) (43) developed an online risk calculator based on childhood characteristics to predict adult ADHD and achieved similar performance in the generating sample (AUC for predicting adult ADHD, 0.82; 95% CI, 0.79–0.83). Their risk calculator included the following predictors: sex, socioeconomic status, single-parent family, ADHD symptoms, comorbid disruptive disorders, childhood maltreatment, maternal depression, and Intelligence Quotient (IQ).

Certain limitations should be considered in our findings. First, we assessed children around the age of 6 because this was the maximum duration of postnatal follow-up at our center. This may not be long enough to identify all children with ADHD, or may have underestimated children with the inattentive type, which is usually identified at elementary school years (44). To minimize this, we performed a full clinical diagnostic assessment confirmed by DSM-IV criteria and found a high ADHD diagnostic rate in our sample (33.33%). Second, the R^2 result of 34.9% in the analysis indicates that much of the variance in the performance ratings remained unexplained, suggesting that other, unavailable genetic, gestational and neonatal data should play a role in ADHD risk. Third, maternal ASRS-18 score was collected at the same time as the child was evaluated for ADHD (i.e., at around 6 years of age) and not in the perinatal period., However, ADHD symptoms in older adults have shown lifetime

stability (45). Fourth, as we had a small sample size, the model may have selected spurious predictors (i.e., overfitting) (46). Although some authors suggest having at least 10 outcome events per variable (47, 48), some investigators either consider this number too high (49) or advocate that it should not be used at all (50). It is important to highlight that the use of LASSO technique minimized this potential shortcoming. Fifth, development of the risk calculator for ADHD prediction was carried out in a middle/low-income country, and generalization to high-income countries may not be possible.

CONCLUSION

From a clinical perspective, our risk calculator represents a potential practical tool for early identification of VP/VLBW children at high risk for future ADHD diagnosis. This instrument can be used by pediatricians, primary care physicians, and any other clinicians who care for this population. With better risk estimation, clinicians can select patients who will benefit from closer monitoring. Moreover, early identification of ADHD symptoms can enable early preventive and treatment interventions in order to delay ADHD onset or reduce impairments in school, work, and relationships.

From a research point of view, future studies should focus on (1) replicating the risk calculator in larger, longitudinal prospective samples; (2) carrying out external validation elsewhere in the world; (3) evaluating the effectiveness of risk stratification provided by the calculator; (4) developing preventive interventions against ADHD development in high risk VP/VLBW newborns, and (5) clarifying the potential pathophysiological mechanisms which underlie ADHD predictors, in the search for strategies to minimize VP/VLBW burden.

SUPPLEMENTARY INFORMATION

Abbreviations

ADHD: Attention-deficit/hyperactivity disorder
ASRS-18: Adult ADHD Self-Report Scale
AUC: Area under de curve
CI: Confidence interval
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders fourth edition
ELBW: Extremely low birth weight
EP: Extremely preterm
HCPA: Hospital de Clínicas de Porto Alegre
HIV: Human immunodeficiency virus
IQ: Intelligence quotient
LASSO: Least absolute shrinkage and selection operator
NICU: Neonatal intensive care unit
OR: Odds ratio
ROC: Receiver operating characteristic
SD: Standard deviation
SNAPPE-II: Score for Neonatal acute Physiology with Perinatal Extension-II
STORCH: Syphilis, toxoplasmosis, rubella, cytomegalovirus, or herpesvirus
TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
VLBW: Very low birth weight
VP: Very preterm
WHO: World Health Organization

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Contributor's Statement

Adelar Pedro Franz conceptualized and designed the study, helped in data collection, conducted clinical interviews with mother-child pairs, and drafted the initial manuscript.

Arthur Caye carried out the analyses and reviewed the manuscript.

Bárbara Calil Lacerda and Flávia Wagner helped with data collection and reviewed the manuscript.

Rita C Silveira and Renato Soibelmann Procianoy helped with data collection and critically reviewed the manuscript.

Carlos Renato Moreira-Maia conceptualized and designed the study, helped with data collection, and reviewed the manuscript.

Luis Augusto Rohde conceptualized and designed the study and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

1. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global health. 2019;7(1):e37-e46.

2. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. The Lancet Global health. 2019;7(7):e849-e60.

3. Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E. Deaths: Final Data for 2016. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2018;67(5):1-76.

4. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Langstrom N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. JAMA psychiatry. 2013;70(11):1231-40.

5. Tucker J, McGuire W. Epidemiology of preterm birth. Bmj. 2004;329(7467):675-8.

6. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

7. Martin, J. A., Hamilton, B. E., Osterman, M. J., Curtin, S. C., & Matthews, T. J. (2015). Births: final data for 2013. National vital statistics reports: from the

centers for disease control and prevention, national center for health statistics, national vital statistics system, 64, 1–65.

8. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009;124(2):717-28.

9. McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: a systematic review. Pediatrics. 2011;127(6):1111-24.

10. American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.

11. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. Journal of child psychology and psychiatry, and allied disciplines. 2015;56(3):345-65.

12. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. The American journal of psychiatry. 2007;164(6):942-8.

13. Serati M, Barkin JL, Orsenigo G, Altamura AC, Buoli M. Research Review: The role of obstetric and neonatal complications in childhood attention deficit and hyperactivity disorder - a systematic review. Journal of child psychology and psychiatry, and allied disciplines. 2017;58(12):1290-300.

14. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. Pediatrics. 2018;141(1).

15. O'Shea TM, Downey LC, Kuban KK. Extreme prematurity and attention deficit: epidemiology and prevention. Frontiers in human neuroscience. 2013;7:578.

16. Burnett AC, Anderson PJ, Cheong J, Doyle LW, Davey CG, Wood SJ. Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. Psychological medicine. 2011;41(12):2463-74.

17. Dammann O, O'Shea TM. Cytokines and perinatal brain damage. Clinics in perinatology. 2008;35(4):643-63, v.

18. Hagberg H, Peebles D, Mallard C. Models of white matter injury: comparison of infectious, hypoxic-ischemic, and excitotoxic insults. Mental retardation and developmental disabilities research reviews. 2002;8(1):30-8.

19. Coghill D, Nigg J, Rothenberger A, Sonuga-Barke E, Tannock R. Whither causal models in the neuroscience of ADHD? Developmental science. 2005;8(2):105-14.

20. Shaw M, Hodgkins P, Caci H, Young S, Kahle J, Woods AG, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. BMC medicine. 2012;10:99.

21. Langley K, Fowler T, Ford T, Thapar AK, van den Bree M, Harold G, et al. Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. The British journal of psychiatry : the journal of mental science. 2010;196(3):235-40.

22. Bernardini F, Attademo L, Cleary SD, Luther C, Shim RS, Quartesan R, et al. Risk Prediction Models in Psychiatry: Toward a New Frontier for the Prevention of Mental Illnesses. The Journal of clinical psychiatry. 2017;78(5):572-83.

23. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Annals of internal medicine. 2015;162(1):55-63.

24. Brasil HH, Bordin IA. Convergent validity of K-SADS-PL by comparison with CBCL in a Portuguese speaking outpatient population. BMC psychiatry. 2010;10:83.

25. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry. 1997;36(7):980-8.

26. Hines JL, King TS, Curry WJ. The adult ADHD self-report scale for screening for adult attention deficit-hyperactivity disorder (ADHD). Journal of the American Board of Family Medicine : JABFM. 2012;25(6):847-53.

27. Mattos P, Segenreich D, Saboya E, Louzã M, Dias G, Romano M. Adaptação transcultural para o português da escala Adult Self-Report Scale para avaliação do transtorno de déficit de atenção/hiperatividade (TDAH) em adultos. Rev. psiquiatr. clín. 2006; 33(4):188-194.

28. Buuren SV, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011;45(3):1-67.

29. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2013.

30. Pavlou M, Ambler G, Seaman SR, Guttmann O, Elliott P, King M, et al. How to develop a more accurate risk prediction model when there are few events. Bmj. 2015;351:h3868.

31. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. Journal of Statistical Software. 2010;33(1):1-22.

32. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. Bmj. 2016;352:i6.

33. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. Jama. 2015;313(4):409-10.

34. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Molecular psychiatry. 2019;24(4):562-75.

35. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. Current psychiatry reports. 2017;19(1):1.

36. Bhattacharya A, Derecki NC, Lovenberg TW, Drevets WC. Role of neuro-immunological factors in the pathophysiology of mood disorders. Psychopharmacology. 2016;233(9):1623-36.

37. Anand D, Colpo GD, Zeni G, Zeni CP, Teixeira AL. Attention-Deficit/Hyperactivity Disorder And Inflammation: What Does Current Knowledge Tell Us? A Systematic Review. Frontiers in psychiatry. 2017;8:228.

38. Dunn GA, Nigg JT, Sullivan EL. Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. Pharmacology, biochemistry, and behavior. 2019;182:22-34.

39. Oades RD, Dauvermann MR, Schimmelmann BG, Schwarz MJ, Myint AM. Attention-deficit hyperactivity disorder (ADHD) and glial integrity: S100B, cytokines and kynurenine metabolism--effects of medication. Behavioral and brain functions : BBF. 2010;6:29.

40. O'Shea TM, Joseph RM, Kuban KC, Allred EN, Ware J, Coster T, et al. Elevated blood levels of inflammation-related proteins are associated with an attention problem at age 24 mo in extremely preterm infants. Pediatric research. 2014;75(6):781-7.

41. Hafeman DM, Merranko J, Goldstein TR, Axelson D, Goldstein BI, Monk K, et al. Assessment of a Person-Level Risk Calculator to Predict New-Onset Bipolar

Spectrum Disorder in Youth at Familial Risk. JAMA psychiatry. 2017;74(8):841-7.

42. Schwenke E, Fasching PA, Faschingbauer F, Pretscher J, Kehl S, Peretz R, et al. Predicting attention deficit hyperactivity disorder using pregnancy and birth characteristics. Archives of gynecology and obstetrics. 2018;298(5):889-95.

43. Caye A, Agnew-Blais J, Arseneault L, Goncalves H, Kieling C, Langley K, et al. A risk calculator to predict adult attention-deficit/hyperactivity disorder: generation and external validation in three birth cohorts and one clinical sample. Epidemiology and psychiatric sciences. 2019:1-9.

44. Chien IC, Lin CH, Chou YJ, Chou P. Prevalence, incidence, and stimulant use of attention-deficit hyperactivity disorder in Taiwan, 1996-2005: a national population-based study. Social psychiatry and psychiatric epidemiology. 2012;47(12):1885-90.

45. Semeijn EJ, Comijs HC, de Vet HC, Kooij JJ, Michielsen M, Beekman AT, et al. Lifetime stability of ADHD symptoms in older adults. Attention deficit and hyperactivity disorders. 2016;8(1):13-20.

46. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. Medical decision making : an international journal of the Society for Medical Decision Making. 2001;21(1):45-56.

47. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. Journal of clinical epidemiology. 1995;48(12):1503-10.

48. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. Journal of clinical epidemiology. 1996;49(12):1373-9.

49. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. American journal of epidemiology. 2007;165(6):710-8.

50. Courvoisier DS, Combescure C, Agoritsas T, Gayet-Ageron A, Perneger TV. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. Journal of clinical epidemiology. 2011;64(9):993-1000.

51. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC pediatrics. 2013;13:59.

Figures

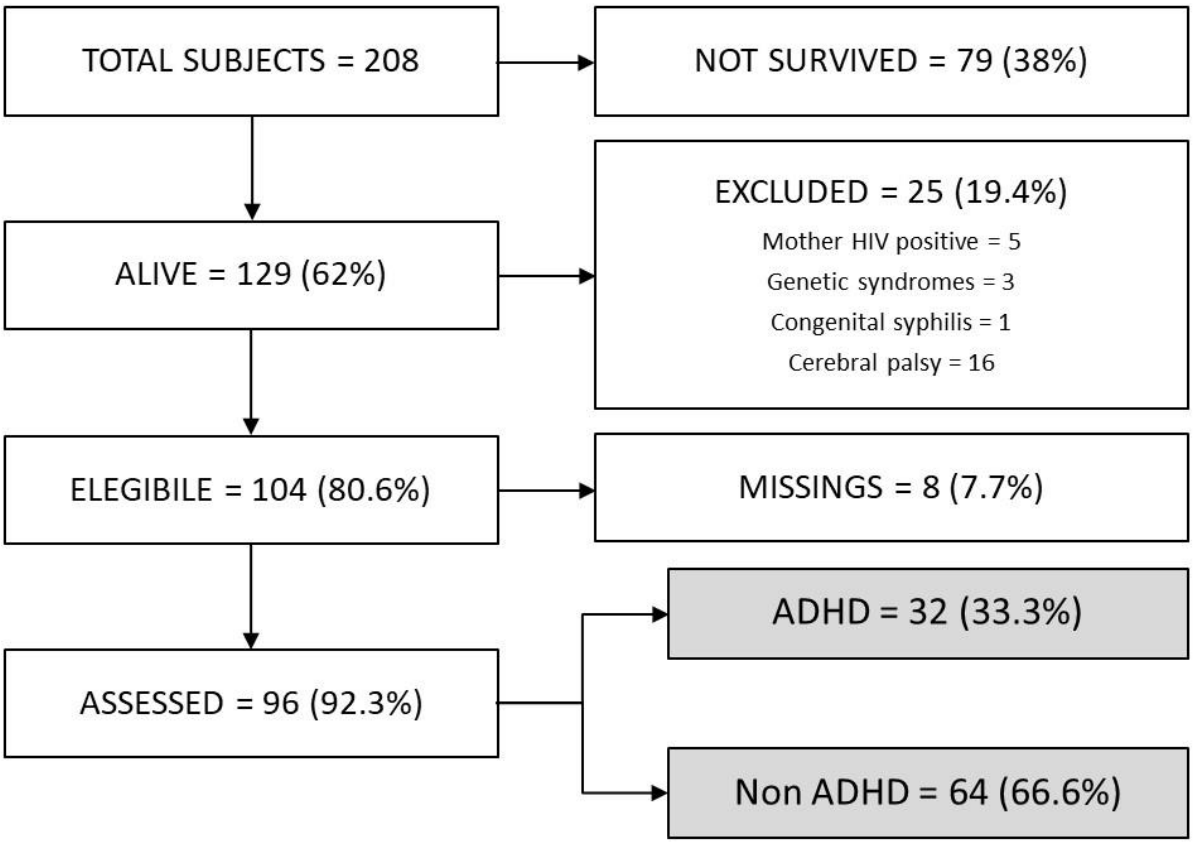


FIGURE 1: Participant flow diagram.

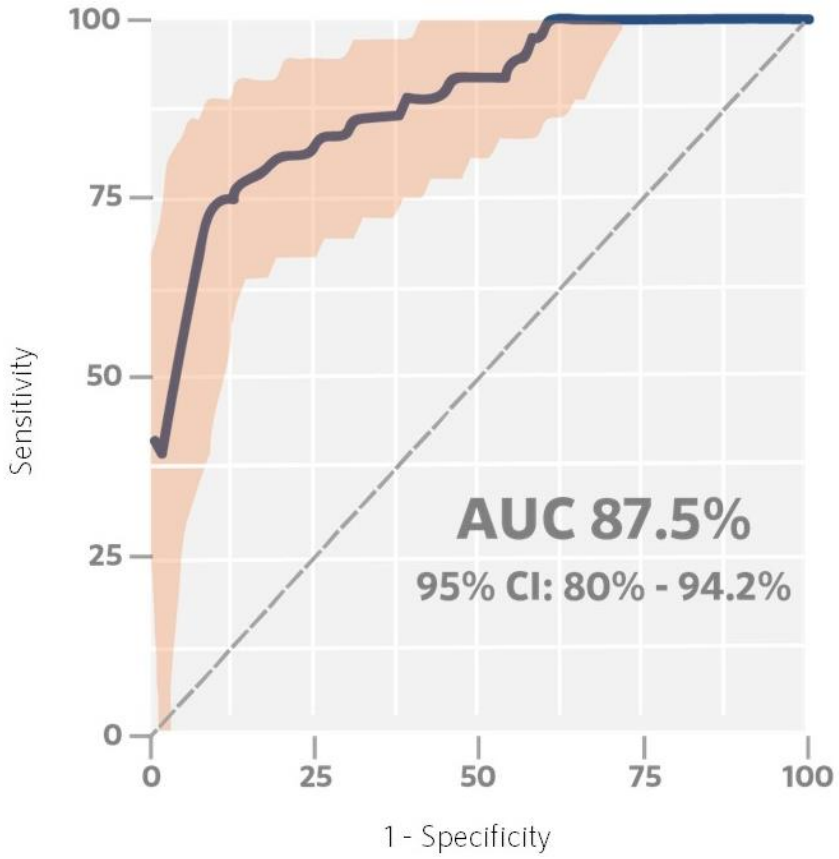


FIGURE 2: Area under the receiver operating characteristic (ROC) curve.

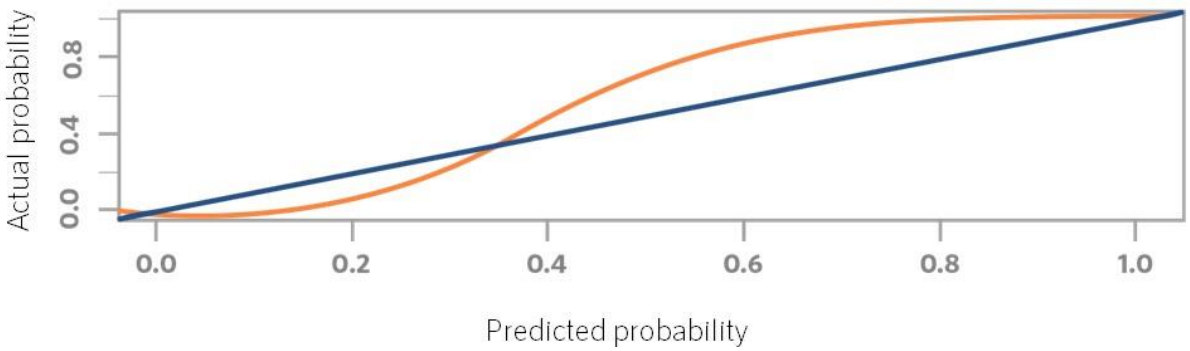


FIGURE 3: Calibration plot corrected by bootstrapping. The diagonal line represents perfect calibration.

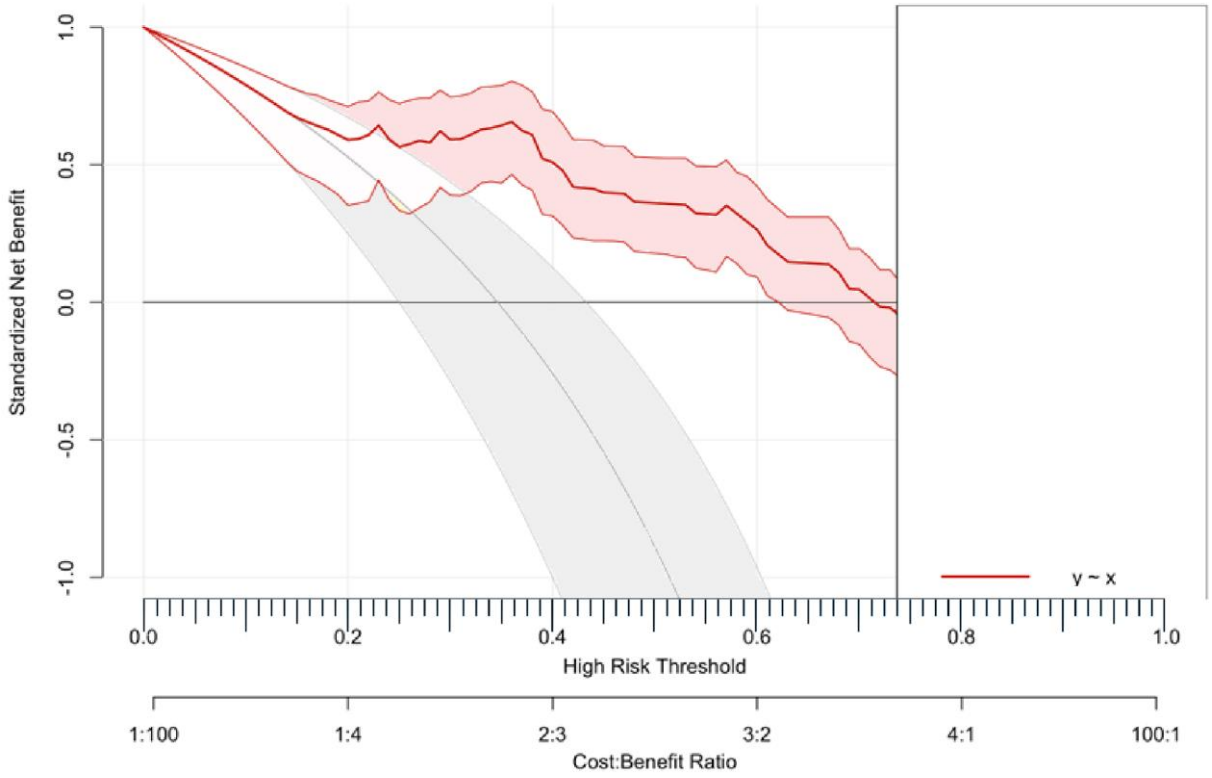


FIGURE 4: Estimated decision curve analysis – the red line and its confidence interval shows the clinical usefulness (net benefit) of using the risk calculator for management compared to a “treat all” or “treat none” approach (gray line) over a range of high-risk thresholds for ADHD at around the age of 6.

Tables

TABLE 1: Gestational and neonatal variables and outcomes.

Continuous variables	N	Range	Mean	SD
Apgar score at 1 minute after birth	104	(1-9)	5.87	2.52
Apgar score at 5 minutes after birth	104	(2-10)	8.21	1.42
Birth weight (grams)	104	(640-1565)	1156.73	230.45
Gestational age (weeks)	104	(24.4-36)	30.19	2.51
Head circumference at discharge (z score)	101	(-3.6-2.5)	-0.73	0.96
Length of hospital stay (days)	103	(23-233)	62.15	33.00
SNAPPE II	104	(0-69)	13.96	14.48
Total parenteral nutrition time (days)	104	(0-86)	16.14	16.66
Maternal ASRS score	94	(1-53)	20.93	10.64
Categorical variables	**N**	**Yes n (%)**		
Gestational variables				
Chronic arterial hypertension	102	16 (15.69)		
Gestational diabetes mellitus	104	5 (4.81)		
Low socioeconomic status	98	15 (15.31)		
Pre-eclampsia	102	22 (21.57)		
Prolonged rupture of membranes	102	20 (19.61)		
STORCH	101	32 (31.68)		
Urinary tract/ovarian infection	104	25 (24.04)		
Neonatal variables				
Bronchopulmonary dysplasia	103	31 (30.10)		
Chorioamnionitis	102	13 (12.75)		
Delayed birth weight recovery	103	25 (24.27)		
Hypoglycemia	100	12 (12.00)		
Late-onset sepsis confirmed by blood culture	103	26 (25.24		
Male sex	104	51 (49.04)		
Mechanical ventilation	104	54 (51.92)		
Necrotizing enterocolitis	103	10 (9.71)		
Neonatal seizures	104	37 (35.58)		
Peri-intraventricular hemorrhage grade 2, 3, or 4	102	5 (4.90)		
Periventricular leukomalacia	102	14 (13.73)		
Respiratory distress syndrome	104	51 (49.04)		
Retinopathy of prematurity	91	10 (10.99)		
Small for gestational age	103	55 (53.40)		
Transient tachypnea of the newborn	104	5 (4.81)		
Categorical outcomes	**N**	**Yes n (%)**		
Main				
ADHD diagnosis	96	32 (33.33)		
Test				

Anxiety disorder (any)	96	26 (27.08)
Oppositional defiant disorder	96	23 (23.96)

ASRS: ADHD Self-Report Scale; SD: Standard deviation; SNAPPE II: Score for Neonatal Acute Physiology with Perinatal Extension-II; STORCH: syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpesvirus

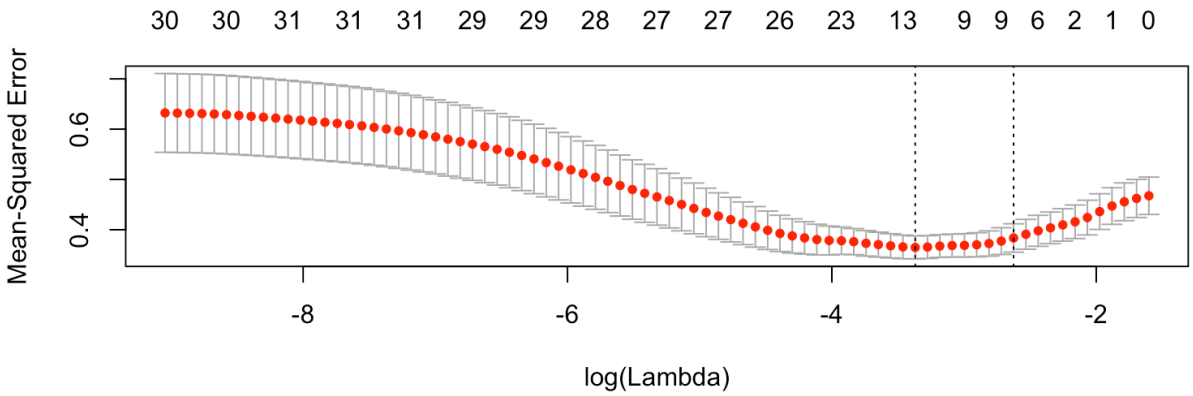
TABLE 2: Prediction model specifications.

Selected predictors	Predictor value	Regression coefficient	Odds ratio
Categorical Variables			
Late-onset sepsis confirmed by blood culture	0 or 1	0.099882617	1.105041197
Necrotizing enterocolitis	0 or 1	0.160930548	1.174603387
Neonatal seizures	0 or 1	0.11643877	1.123488717
Periventricular leukomalacia	0 or 1	1.649606845	5.204933078
Respiratory distress syndrome	0 or 1	0.357910082	1.430337002
Continuous Variables			
Maternal ASRS score	0-72 points	0.032105519	1.032626462
Length of hospital stay	number of days	0.00060327	1.000603452
Model Intercept		**-1.879676438**	
RISK SCORE FORMULA*	(-1.879676438) + (0.099882617 × late-onset sepsis confirmed by blood culture) + (0.11643877 × neonatal seizures) + (0.160930548 × necrotizing enterocolitis) + (1.649606845 × periventricular leukomalacia) + (0.357910082 × respiratory distress syndrome) + (0.00060327 × length of hospital stay in days) + (0.032105519 × maternal ASRS-18 score) =		
ADHD RISK (%) FORMULA	= 100 / (1+exp(-(RISK SCORE)		
ONLINE ADHD RISK CALCULATOR	https://jscalc.io/calc/unaQG5TuvzVzuzmV		

* Predictor value is 1 when present and zero when absent. ADHD: Attention-deficit/hyperactivity disorder; ASRS: ADHD Self-Report Scale.

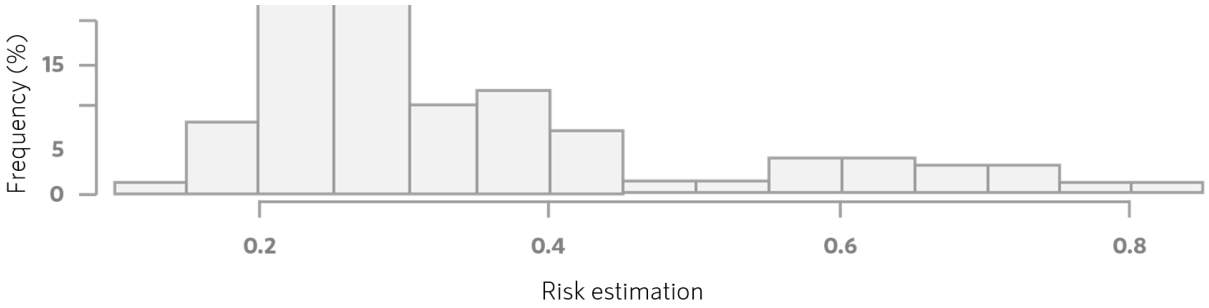
Supplementary Figures:

SUPPLEMENTARY FIGURE 1: Cross-validation procedure.

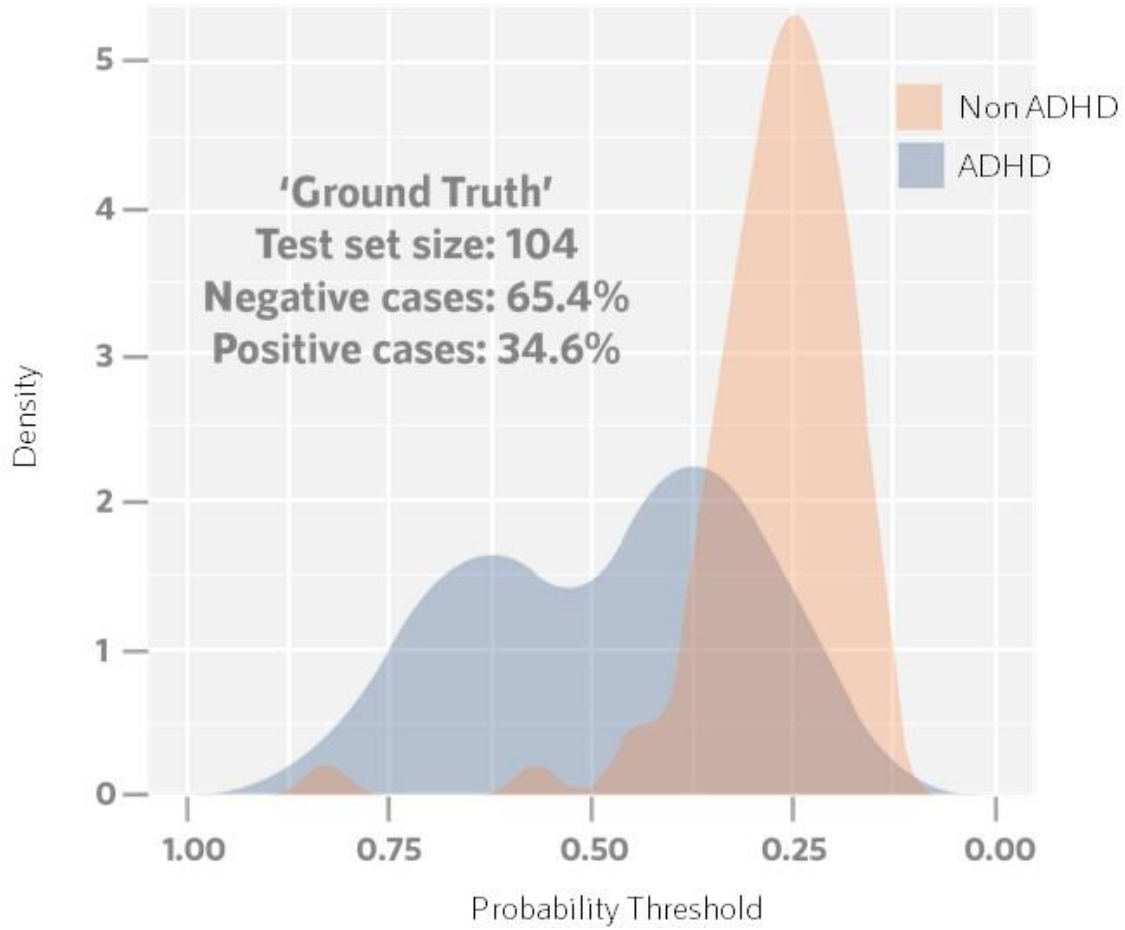


Upper horizontal row: number of selected predictors
First vertical dotted line: lambda with the lowest mean-squared error
Second vertical dotted line: 1 standard deviation lambda

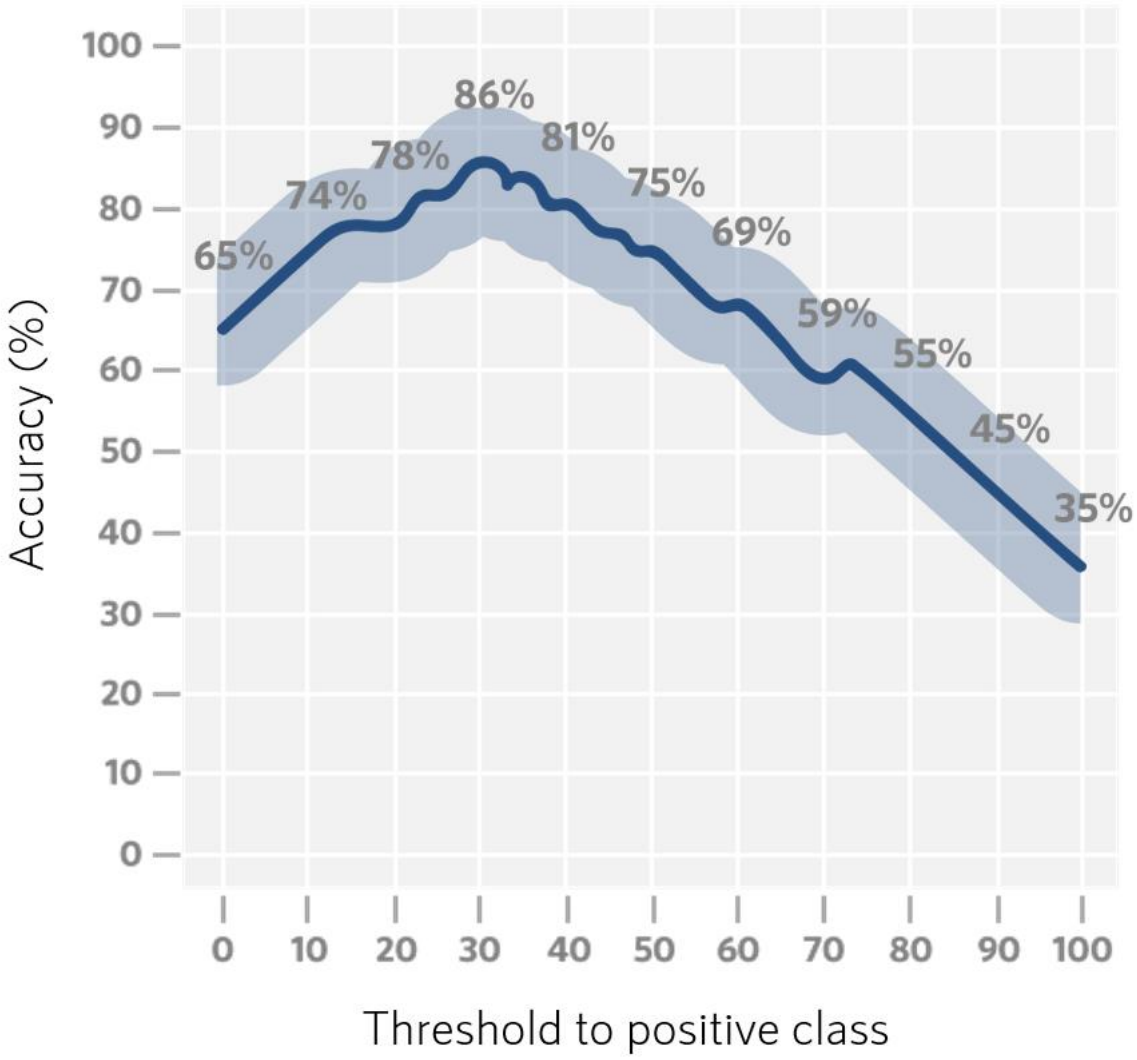
SUPPLEMENTARY FIGURE 2: Lambda selection process.



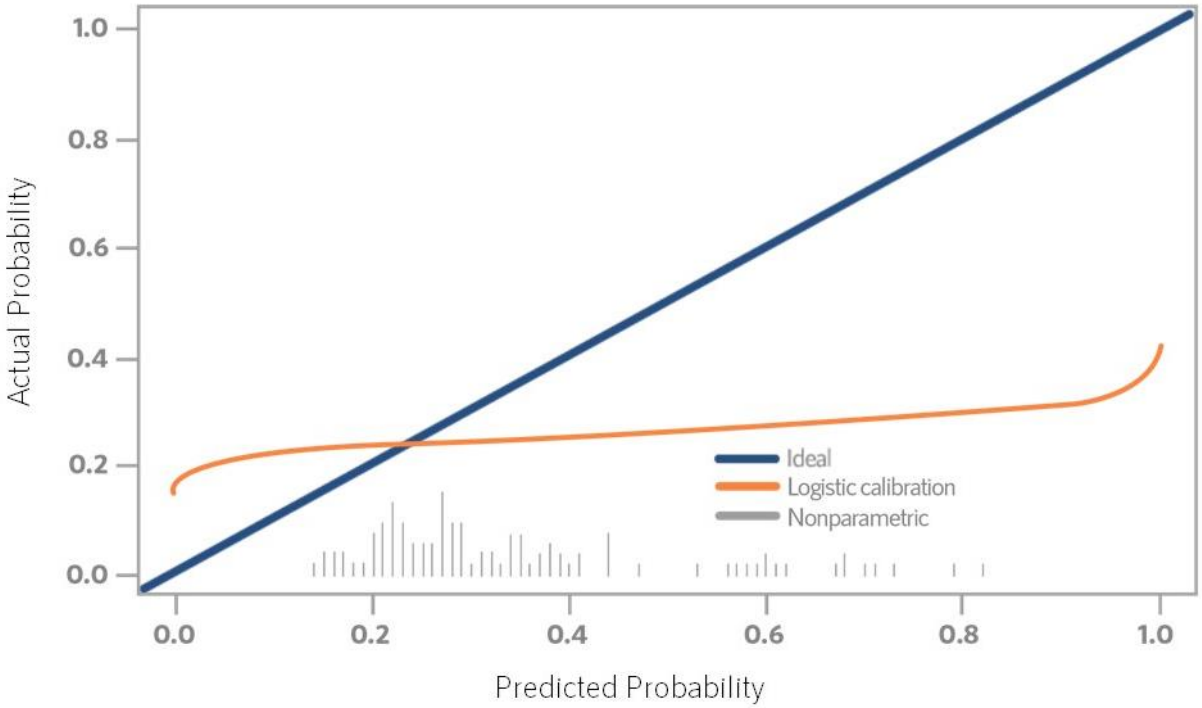
SUPPLEMENTARY FIGURE 3: Frequency of ADHD across risk estimates in the sample.



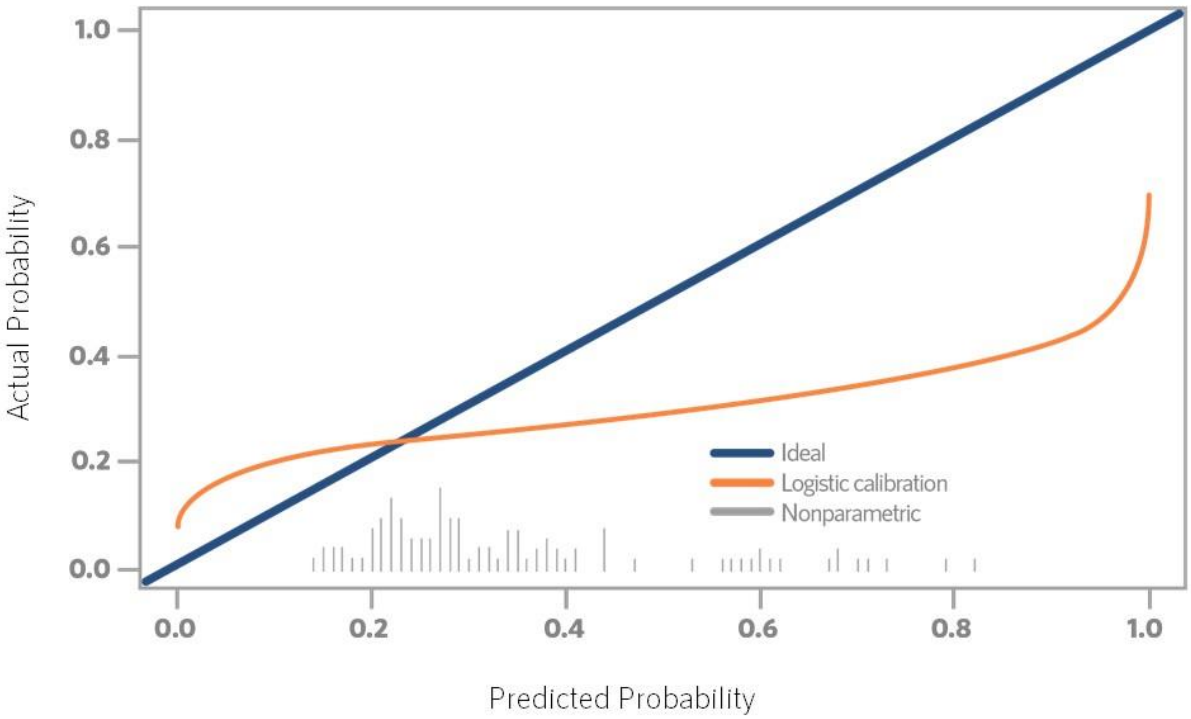
SUPPLEMENTARY FIGURE 4: Prediction density plot of ADHD and non-ADHD individuals over a range of probability thresholds.



SUPPLEMENTARY FIGURE 5: Accuracy of prediction over a range of threshold to positive class.



SUPPLEMENTARY FIGURE 6: Calibration plot for anxiety disorders. The diagonal line represents perfect calibration.



SUPPLEMENTARY FIGURE 7: Calibration plot for oppositional defiant disorder. The diagonal line represents perfect calibration.

Supplementary Tables:

SUPPLEMENTARY TABLE 1: Key study characteristics.

Data collection period	October 2015 to September 2017
Study design	Retrospective cohort
Setting	NICU at a tertiary care university hospital in Porto Alegre, Brazil
Inclusion criteria	All VP and/or VLBW patients born from January 2010 to December 2012
Exclusion criteria	HIV-positive mother Newborn with genetic syndrome Newborn with congenital infection Newborn with cerebral palsy
Outcome	Attention deficit/hyperactivity disorder (categorical diagnosis)
Test Outcome 1	Anxiety disorder (any) (categorical diagnosis)
Test Outcome 2	Oppositional defiant disorder (categorical diagnosis)
Reference standard for outcomes	K-SADS-PL

NICU: Neonatal intensive care unit; K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version; VLBW: very Low birth weight; VP: very preterm; HIV: human immunodeficiency viruses.

SUPPLEMENTARY TABLE 2: Risk factors definitions.

Continuous variables	
Apgar score at 1 minute after birth	A rating of 0, 1, or 2 for each of five characteristics at 1 minute after birth: skin color, heart rate, response to stimulation of the sole of the foot, muscle tone, and respiration, with 10 being a perfect score.
Apgar score at 5 minutes after birth	A rating of 0, 1, or 2 for each of five characteristics at 5 minutes after birth: skin color, heart rate, response to stimulation of the sole of the foot, muscle tone, and respiration, with 10 being a perfect score.
Birth weight	Body weight at birth in grams.
Gestational age	Age of pregnancy by obstetric ultrasonography in weeks.
Head circumference at discharge	Distance from the most prominent part of the forehead around to the widest part of the back of the head using a measuring tape, expressed as z score on the Fenton growth chart for preterm infants.[23601190]
Length of hospital stay	Calculated by subtracting the day of birth from the day of hospital discharge.
SNAPPE II	Score for Neonatal Acute Physiology-Perinatal Extension II: a score based on the lowest mean blood pressure, the lowest temperature, the smallest partial pressure of oxygen in arterial blood/fractional concentration of inspired oxygen (PaO_2/FiO_2), lowest negative logarithm of the hydrogen ion concentration (pH), seizures, urinary output, birth weight, low Apgar score, and small for gestational age.
Total parenteral nutrition time	Time in days of nutritional support given intravenously alone.
Maternal ASRS-18 score	ADHD Adult Self-Report Scale (ASRS) score, based on the sum of item scores for all 18 DSM-IV Criterion A symptoms of adult ADHD. Each of these items is scored based on the frequency of the symptom (never = 0 point, rarely = 1 point, sometimes = 2 points, often = 3 points, very often = 4 points). The minimum score is 0, and the maximum score is 72.
Categorical variables	
Gestational variables	
Chronic arterial hypertension	Blood pressure exceeding 140/90 mmHg before pregnancy or before 20 weeks' gestation.
Gestational diabetes mellitus	Glucose intolerance with onset or first recognition during pregnancy.
Low socioeconomic status	Belonging to class D or E according to the Brazilian economic classification criteria (Critério Brasil) developed by the Brazilian Market Research Association (ABEP), based on ownership of eight types of durable goods, employment of domestic workers, and level of education attained by the head of household. Available at http://www.abep.org/criterio-brasil.
Pre-eclampsia	A hypertensive syndrome that occurs in pregnant women after 20 weeks of gestation and consists of persistent, recent-onset

	hypertension (defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, based on at least two measurements taken at least 4 hours apart) with one or more of the following conditions: 1) proteinuria (defined as urinary excretion of ≥0.3 g protein every 24 hours); 2) evidence of systemic involvement, such as renal failure (elevated creatinine), hepatic impairment (elevated transaminases and/or right upper quadrant pain), neurological complications, hematological complications; 3) fetal growth restriction.
Prolonged rupture of membranes	Pre-labor rupture of membranes in which more than 18 hours have passed between rupture and onset of labor.
STORCH	Maternal diagnosis of syphilis, toxoplasmosis, rubella, cytomegalovirus, or herpesvirus during gestation.
Urinary tract/ovarian infection	Confirmed maternal urinary tract infection or ovarian infection during gestation.
Neonatal	
Bronchopulmonary dysplasia	Need for oxygen for at least 28 days with typical lung radiographic changes.
Chorioamnionitis	Maternal fever and at least two of the following: maternal leukocytosis, maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of amniotic fluid.
Delayed birth weight recovery	Failure to regain birth weight after 14 days of life.
Hypoglycemia	Serum glucose concentration <30 mg/dL (<1.7 mmol/L) in the preterm infant.
Late-onset sepsis confirmed by blood culture	Sepsis presenting after the 72nd hour of life, confirmed by blood culture.
Male sex	Sex assignment at birth by inspection of the genitalia when the baby is delivered.
Mechanical ventilation	Assisted artificial ventilation where mechanical means are used to assist or replace spontaneous breathing.
Necrotizing enterocolitis	Clinical features (abdominal distention, bilious vomiting or gastric aspirate, and rectal bleeding) and abdominal imaging of intramural gas, pneumoperitoneum, or hepatobiliary gas.
Neonatal seizures	Clinical signs confirmed by electroencephalographic (EEG) features.
Peri-intraventricular hemorrhage grade 2, 3, or 4	Intraventricular hemorrhage that occupies at least 10 to 50 percent (grade 2) or more than 50 percent (grade 3) of the lateral ventricle volume; or periventricular hemorrhagic infarction (grade 4).
Periventricular leukomalacia	Cystic periventricular leukomalacia and white-matter lesions, defined by cranial ultrasonography and magnetic resonance imaging at term equivalent.
Respiratory distress syndrome	Onset of progressive respiratory failure shortly after birth (manifested by an increase in the work of breathing and an increase in the oxygen requirement), in conjunction with characteristic chest radiograph findings.
Retinopathy of prematurity	Disorganized growth of retinal blood vessels assessed by ophthalmologic eye examination.

Small for gestational age	Birth weight below the 10th percentile for gestational age.
Transient tachypnea of the newborn	Tachypnea (respiratory rate greater than 60 breaths per minute) within two hours after delivery.

8. CONSIDERAÇÕES FINAIS

Dada a proporção aumentada de crianças nascendo e sobrevivendo ao parto prematuro e ao baixo peso ao nascer, as consequências a longo prazo para os indivíduos e a sociedade devem ser abordadas. Esta tese de doutorado teve como resultado a produção de 2 artigos científicos, um dos quais se encontra publicado e o segundo encontra-se pronto para submissão.

O primeiro artigo realizou uma revisão sistemática e meta-análise, onde avaliamos o risco de indivíduos MP/MBPN e EP/EBPN em desenvolver TDAH, enfatizando diagnósticos categóricos e dimensionais bem definidos e fornecendo evidências de associações robustas. Em 12 estudos de diagnóstico categórico em que os pesquisadores avaliaram um total de 1.787 indivíduos, sugeriu-se que indivíduos MP/MBPN e EP/EBPN tenham aproximadamente 3 vezes mais chances de serem diagnosticados com TDAH do que controles nascidos a termo. No grupo MP/MBPN, essa probabilidade foi aproximadamente duplicada, enquanto no grupo EP/EBPN foi aumentada quatro vezes. Esse aumento de risco de TDAH de aproximadamente 300% talvez seja o fator de risco ambiental mais forte para o TDAH de qualquer tipo (biológico ou ambiental) até agora descrito.

Ainda no artigo 1, em 29 estudos sobre sintomas de TDAH envolvendo um total de 3.504 indivíduos, demonstramos que os sintomas de desatenção e hiperatividade/impulsividade estão associados de maneira semelhante aos recém-nascidos MP/MBPN, com grandes tamanhos de efeito encontrados para as dimensões de desatenção e tamanhos de efeito moderados para hiperatividade/impulsividade.

Já no segundo artigo, construímos uma calculadora de risco fácil de usar para prever, entre os recém-nascidos MP/MBPN, o risco de desenvolver o diagnóstico de TDAH cerca de 6 anos depois. Constatamos que a combinação do número total de sintomas de TDAH da mãe e alguns dados categóricos neonatais (tempo de internação, sepse tardia confirmada por hemocultura, enterocolite necrosante, convulsões neonatais, leucomalácia periventricular e síndrome do desconforto respiratório) alcançaram bom desempenho para discriminar entre aqueles que

desenvolverão TDAH vs. aqueles que não o farão. O modelo mostrou especificidade para o TDAH em comparação com outras psicopatologias infantis comuns (Transtornos de Ansiedade e Transtorno de Oposição e Desafio).

Do ponto de vista clínico, a calculadora de risco representa uma ferramenta prática para a identificação precoce de crianças MP/MBPN com alto risco para diagnóstico futuro de TDAH. Este instrumento pode ser usado por pediatras, médicos de cuidados primários e quaisquer outros médicos que cuidam desses pacientes. Tendo uma melhor estimativa de risco, os médicos podem selecionar pacientes que necessitem de um monitoramento mais de perto. Além disso, a identificação precoce dos sintomas do TDAH pode possibilitar intervenções preventivas e de tratamento precoces, a fim de reduzir o aparecimento ou comprometimento do TDAH na família, na escola, no trabalho e nos relacionamentos. A criação de intervenções de caráter preventivo específicas para as famílias, para as gestantes, para os neonatos e para as crianças são necessárias para minimizar os efeitos da prematuridade, do baixo peso ao nascer e, consequentemente do TDAH.

Do ponto de vista da pesquisa, estudos futuros devem se concentrar em replicar a calculadora de risco em amostras populacionais de maior escala, realizar validações externas em outros países e avaliar a eficácia na estratificação de risco da calculadora. Além disso, é necessário esclarecer os mecanismos fisiopatológicos por trás dos fatores de risco pré-natais e neonatais para TDAH, tanto genéticos quanto ambientais, para melhorar nossa compreensão da etiologia do TDAH e para desenvolver estratégias de prevenção e intervenção clinicamente apropriadas para minimizar a morbidade das crianças MP/MBPN.

9. ANEXOS

9.1 COMENTÁRIO PUBLICADO DO ARTIGO 1

ADHD and Early Experience: Revisiting the Case of Low Birth Weight

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DOI: https://doi.org/10.1542/peds.2017-3488
PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Abbreviations

ADHD: attention-deficit/hyperactivity disorder
LBW: low birth weight
PM: premature

The improving survival rates of extremely low, very low, and low birth weight (LBW) and premature (PM) infants are good news. Scientifically, they raise complex questions about trends in the incidence of neurodevelopmental conditions (1), from severe injuries like cerebral palsy, now declining after earlier increases in incidence (2), to subtler yet also disabling and costly conditions like attention-deficit/hyperactivity disorder (ADHD), whose true incidence likewise may not have increased in the past 15 years (3).

In the accompanying meta-analysis by Franz et al (4), the magnitude of the association of LBW/PM with ADHD is striking; at a risk increase of ~300%, it is perhaps

the strongest single risk factor for ADHD of any type (biological or environmental) now known. At this effect size, LBW/PM would characterize a substantial portion of ADHD cases. Researchers of ADHD populations who can clarify how many patients had LBW/PM, and who can include more in-depth characterization of ADHD than was possible in many of the studies included by Franz et al (4) will help to determine how well these findings generalize across different sampling approaches.

LBW is multiply determined, but it also has modest heritability (5). The authors of studies of LBW have rarely if ever considered causally informative designs (6) to take into account genotype-environment correlation or other unmeasured third causes of both LBW/PM and ADHD. For example, a study of surrogate mothers revealed that much of maternal smoking's association with offspring ADHD is accounted for by genotype-environment correlation (7). Thus, causal inferences should be made cautiously here. However, the modest heritability of LBW compared with ADHD could suggest that the direct effect of LBW/PM on ADHD cannot be accounted for entirely by genotype-environment correlation. Thus, with their findings, Franz et al (4) underscore the commonplace understanding that ADHD is not determined simply by heredity, but more likely by the interplay of genetic and environmental dynamics, and that the disorder may ultimately be understood as an epigenetic condition (8,9).

It is possible that many informative studies were excluded from the meta-analysis, and the authors note other limitations (heterogeneity of effect sizes, pooling across time and nation). We also note that the many important contributors to LBW/PM, such as maternal smoking, were, perhaps necessarily, beyond the scope of the current report. Yet, it is unlikely that these concerns would overturn the present findings. For example, LBW is associated with ADHD even when maternal smoking is considered in a comparison of LBW and children with normal birth weight (10).

The magnitude of the observed association raises several additional questions. First, how specific is this linkage to ADHD? As the authors document, other conditions besides ADHD can arise from LBW/PM, but, apparently, few study authors have looked at ADHD and other conditions together in the same cohort. It may be that the effect size is similar for ADHD as for anxiety or other conditions, but this is unclear when one considers their frequent overlap. If the association with ADHD is reliably

larger than with other developmental conditions, why would this be? Does LBW/PM primarily confer greater susceptibility to whatever follows, and if so, then how is what follows ultimately determined? Crucially, how do some children at risk because of LBW/PM avoid neurodevelopmental harm? Again, of course, genetic susceptibility is likely one important moderator. But early risk further interacts with postnatal experiences, such as caregiver attunement or breastfeeding (11), that may be able to rescue children at risk from LBW/PM, perhaps by epigenetic alterations (12). It will be important to identify such actionable protective mechanisms.

This raises another key question: what are the key mediators in this association? Potentially traceable biological injury is of particular interest. The authors mention some of the many possible biological mechanisms that might mediate this effect but did not attempt to address that question in the current study, probably because of a shortage of comparable studies. In particular, along with the expected influence of genetic susceptibilities, do variable outcomes depend on the particular nature of the injury (e.g., germinal matrix/intraventricular hemorrhage versus parenchymal lesions(13))? Ongoing progress in brain imaging of fetal and neonatal brain structure and function holds considerable promise here.

Of particular interest is understanding the association between LBW/PM and ADHD-related comorbid conditions. For example, how does this association parse in relation to comorbid features of ADHD (besides inattention or hyperactivity as examined here), such as motor development (14) or emotional irritability? As the authors note, the authors of several studies have suggested potential features of ADHD with LBW/PM, including more neurologic problems but less psychiatric comorbidity. It was unfortunate that study variation prevented the authors from being able to pool such effects. This point now warrants much more focused investigation in light of emerging ideas about heterogeneity in ADHD and other disorders.

Overall, the increasing evidence of early-life influences on ADHD requires explanation. It also raises new opportunities for understanding ADHD etiology at the level both of mechanisms and of individual clinical variation. In addition, these types of findings reveal the need for new prospective studies of early development, in which scientists can consider genetic and environmental effects together. In particular, an

approach in which epigenetic change in relation to early experience is examined and in which, when possible, causally informative designs are used (6) could dramatically improve current understanding of ADHD etiology. The coming generation of research on ADHD is likely to include more sophisticated, integrative accounts of how subtle neurodevelopmental injury is involved in child psychiatric conditions such as ADHD.

Footnotes: Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.
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Potential conflict of interest: The authors have indicated they have no potential conflicts of interest to disclose.

Companion paper: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-1645.

References

1. Younge N, Goldstein RF, Bann CM, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Survival and neurodevelopmental outcomes among periviable infants. N Engl J Med. 2017;**376**(7):617–628

2. Durkin MS, Benedict RE, Christensen D, et al. Prevalence of cerebral palsy among 8-year-old children in 2010 and preliminary evidence of trends in its relationship to low birthweight. Paediatr Perinat Epidemiol. 2016;**30**(5):496–510

3. Erskine HE, Ferrari AJ, Nelson P, et al. Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. J Child Psychol Psychiatry. 2013;**54**(12):1263-1274

4. Franz AP, Bolat GU, Bolat H, et al. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics. 2018;**141**(1):e20171645

5. Clausson B, Lichtenstein P, Cnattingius S. Genetic influence on birthweight and gestational length determined by studies in offspring of twins. BJOG. 2000;**107**(3):375–381

6. Lewis SJ, Relton C, Zammit S, Smith GD. Approaches for strengthening causal inference regarding prenatal risk factors for childhood behavioural and psychiatric disorders. J Child Psychol Psychiatry. 2013;**54**(10):1095–1108

7. Thapar A, Rice F, Hay D, et al. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. Biol Psychiatry. 2009;**66**(8):722–727

8. Nigg J. Environment, developmental origins, and attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 2012;**166**(4):387–388

9. Nigg J, Nikolas M, Burt SA. Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2010;**49**(9):863–873

10. Nigg JT, Breslau N. Prenatal smoking exposure, low birth weight, and disruptive behavior disorders. J Am Acad Child Adolesc Psychiatry. 2007;**46**(3):362–369

11. Wazana A, Moss E, Jolicoeur-Martineau A, et al. The interplay of birth weight, dopamine receptor D4 gene (DRD4), and early maternal care in the prediction of disorganized attachment at 36 months of age. Dev Psychopathol. 2015;**27**(4, pt 1):1145–1161

12. Weaver IC, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior. Nat Neurosci. 2004;**7**(8):847–854

13. Whitaker AH, Feldman JF, Lorenz JM, et al. Neonatal head ultrasound abnormalities in preterm infants and adolescent psychiatric disorders. Arch Gen Psychiatry. 2011;**68**(7):742–752

14. Martel MM, Lucia VC, Nigg JT, Breslau N. Sex differences in the pathway from low birth weight to inattention/hyperactivity. J Abnorm Child Psychol. 2007;**35**(1):87–96

9.2 PRODUÇÃO CIENTÍFICA DURANTE O PERÍODO DE DOUTORADO RELACIONADA À TESE

Título: Does ADHD worsen inhibitory control in preschool children born very premature and/or with very low birth-weight?

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Does ADHD worsen inhibitory control in preschool children born very premature and/or with very low birth-weight?

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Abstract

Objective: Evaluate whether ADHD imposes extra inhibitory control (IC) deficits in preschoolers born very premature and/or with very low-birth weight (VP/VLBW).

Methods: 79 VP/VLBW (4 to 7 years) children were assessed for ADHD using KSADS-PL. IC was measured by K-CPT 2 and BRIEF-P.

Results: Significant differences were not found between ADHD (n=24) and non-ADHD children (n=55) for any of the measures (p=0.062 to p=0.903). Both groups had deficits in most K-CPT 2 scores compared to normative samples, indicating poor IC and inconsistent reaction time.

Conclusions: ADHD does not aggravate IC deficits in VP/VLBW children. Either neuropsychological tasks and parent reports on executive functions (EFs) may not be sensitive enough to differentiate VP/VLBW preschoolers with and without ADHD or these children already have such impairments in EFs that there is not much room for additional impairments imposed by ADHD.

Keywords: Inhibitory control. Prematurity. Preschool. ADHD.

INTRODUCTION

Preterm birth is defined as birth occurring before 37 full weeks of gestation. Around the world, its prevalence ranges from 5% to 18% (1)**.** There are sub-categories of preterm birth, based on gestational age: extremely preterm (less than 28 weeks); very preterm (less than 32 weeks); and moderate to late preterm (32 to 37 weeks). According to birth weight, newborns can be classified as very low birth weight (VLBW) (less than 1500 grams), and extremely low birth weight (ELBW) (less than 1000 grams) (2).

Although in recent years the survival rates for very preterm (VP) and VLBW babies have increased due to advances in perinatal and neonatal care (3), death and disability risks are still high for these groups 2. For instance, several structures of the central nervous system may be compromised in VP/VLBW children (4)**.** Alterations in brain structure may in turn translate to neuropsychological deficits in executive functions (3)**.**

Prematurity is frequently associated to neurodevelopmental disorders, such as ADHD (5). ADHD is characterized by inattention and/or hyperactivity/impulsivity interfering with functioning (6). Validity of ADHD diagnosis in preschool children has already been established (7). Overall, neuropsychological studies on preschoolers with ADHD show similar results to those on school-aged children (8)**,** including deficits in response inhibition, delay aversion, working memory, and sustained attention (9,10)**.** Regarding inhibition, preschool children with ADHD tend to present a significantly lower performance in inhibitory control tasks and inventories when compared to those without the disorder (11-13).

Although ADHD is a very common disorder in children born premature and/or at very low birth weight (3, 14), few studies investigated whether ADHD decreases even more inhibitory control performances in premature children. To our knowledge, only one study compared preterm children with and without ADHD using a neuropsychological task. Both neurophysiological and neuropsychological tasks were used, and inhibitory impairments and reaction time variability were found only in

preterm and term children with ADHD (15). It is important to notice, however, that this study has a limited sample of 21 preterm participants.

Based on the literature reviewed above, we aimed to assess if ADHD imposes extra inhibitory control deficit in VP/VLBW preschool children. As ADHD and prematurity are associated to inhibitory control deficits, we hypothesized that premature infants with ADHD would present greater impairment in this function when compared to those without the disorder.

METHODS

Participants

This is a case control study in which preschool children born very prematurely (less than 32 weeks) and/or with very low birth weight (under 1,500 g) diagnosed with ADHD were compared to those without the disorder. The sample included children between 4 and 7 years of age at the time of the assessment who had previously been hospitalized at the Neonatology Service Unit of our University Hospital in Porto Alegre, Brazil. The survivors among those born from January 1st, 2010 to July 31st, 2012 were eligible for the study (n=129). Children diagnosed with either a genetic syndrome, cerebral palsy, or with congenital infections (HIV or syphilis) were excluded from the sample (n=25; see Figure 1). From the final sample (n=104), 2 families refused to participate and 6 could not be located. Finally, data was collected from 96 families. For the purpose of this study children with an IQ lower than 50 and those diagnosed with Bipolar Disorder or Autism Spectrum Disorder were excluded. Thus, our sample was composed by 79 children for whom parents provided valid scores in the BRIEF-P inventory and 70 preschoolers with valid K-CPT 2 scores (see Figure 1).

Data collection and diagnostic procedures

Eligible participants were selected from the Neonatology Service Unit records. They were reached through phone calls, e-mail, mail, social media or home visits. Data

collection occurred at the hospital or at the family residence and took an average of two hours with the parents and 30 minutes with the children. Diagnostic process relied on the use of a semi-structured interview - KSADS-PL (16) **-** administered by a trained child psychiatrist and answered by the child's parents.

Participants verbally agreed to take part in the study, and parents provided written informed consent. This study was approved by the Ethics Committee of the University Hospital - Hospital de Clínicas de Porto Alegre (HCPA).

Neuropsychological assessment

Trained psychologists assessed children in a single session. IQ was estimated through a short version (17) of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (18) composed of four subtests: Block Design, Comprehension, Picture Completion and Arithmetic. Inhibitory control was measured by a computerized task (K-CPT 2) and a behavioral inventory (BRIEF-P) responded by parents or legal guardians. Both instruments are described below:

Conners' Kiddie Continuous Performance Test (K-CPT 2) (19) is a computerized task designed to assess inhibitory control, sustained attention and visual-motor speed. The participant is asked to respond (press the space bar) to all targets presented on a computer screen but refrain from responding to non-targets.

The Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P) evaluates daily behaviors associated with specific domains of executive functioning based on parents' report. Three indexes based on theoretical and empirical factor analytic findings are provided (20): Inhibitory Self-Control Index (ISCI), Flexibility Index (FI) and Emergent Metacognition Index (EMI). A Brazilian translated version was adapted and provided by the Publisher, Psychological Assessment Resources.

Statistical analysis

Descriptive analyses were conducted to characterize the sample. Potential confounders investigated were age, IQ, gender, gestational age, socioeconomic

status, and comorbidities (anxiety disorders and oppositional defiant disorder), using chi-square test for categorical variables and t-test for continuous variables. Those with a p≤0.10 were included in the model (IQ and Oppositional Defiant Disorder). Age was also included because all analyses were conducted with raw scores. K-CPT 2 and BRIEF-P scores were compared through two independent ANCOVAs. The analyses were performed using version 18.0 of the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago, IL, USA) and a p<0.05 was considered significant. Effect size was calculated using partial eta squared and its magnitude defined according to the following interpretation: eta squared <0.06 = small; 0.06-0.14 = medium, >0.14 = large effect size (21). The frequency of cases with a worse performance (>1 standard deviation from normative data) was also calculated and group (ADHD vs. non-ADHD) differences were investigated using chi-square test. Normative scores for both tests were obtained respectively from a Brazilian sample (22) and the original BRIEF-P manual's American sample (20).

RESULTS

Data from 79 participants was analyzed for BRIEF-P scores. Nine participants either refused to finish the K-CPT 2 or the assessment was considered invalid, resulting in a total sample of 70 children with K-CPT 2 data. Demographic and clinical data can be found in Table 1.

Findings emerging from ANCOVAs did not reveal significant differences between ADHD versus non-ADHD groups neither for any of the BRIEF-P scores nor for K-CPT 2 variables (p=0.062 to p=0.903). All effect sizes were small (Table 2). Correlations between K-CPT 2 and BRIEF-P scores were all non-significant and ranged from -0.197 to 0.121.

Frequency of cases with a worse performance (>1 SD from the normative mean) on both instruments was also analyzed. Regarding BRIEF-P scores, 12 children (15.2%) satisfied this condition for the Inhibitory Self-Control Index. For Flexibility and Emergent Metacognition Index, 6 (7.6%) and 17 (21.5%) children respectively were

included in the group with worst performance. No association was found between ADHD and a worse performance in BRIEF-P Indexes (see Table 3).

Regarding a worst K-CPT 2 performance (>1 SD from the normative mean), 69 children (98.6%) fulfilled this condition for the HRT SD index, 60 (85.7%) for variability, 42 (60%) for HRT Block Change and 55 (78.6%) for HRT ISI. The other indexes results were as follows: Omissions 38 (54.3%), Commissions 31 (44.3%), Perseverations 15 (21.4%) and HRT 20 (28.6%) children. We also did not find an association between ADHD and a worse performance in the K-CPT 2 scores (see Table 3).

DISCUSSION

Current evidence shows that deficits in inhibitory control are present both in ADHD (10, 13, 08, 12) and in children born very prematurely (23, 3)**.** However, to our knowledge, only one study compared inhibitory control in VP/VLBW children with and without ADHD. Contrary to our original hypothesis, our results revealed no significant differences in inhibitory control between VP/VLBW children with and without ADHD.

In general, a low correlation is found between executive functions performance tests and behavior scales in the literature (24)**.** The type of selected measurement (behavioral reports or laboratory measures) can also influence the results, either by their intercorrelations or by their associations with ADHD (25). For this reason, we used both a performance measure (K-CPT 2) and a parent rated behavior scale (BRIEF-P). We found consistent results across instruments, indicating no differences between ADHD and non-ADHD groups. Also, as described in the literature, correlations between both types of measures were low.

Given that, we further analyzed whether both groups' results were 1 SD far from the normative mean, expressing a deficit when comparing to the normative samples of K-CPT2 and BRIEF-P. We chose a lenient threshold - one standard deviation or 15,9% out of the normal distribution mean - to identify cases that showed even a mild difficulty. BRIEF-P results indicated that the ADHD group has a slightly higher frequency than that predicted by a normal distribution in Inhibitory Self-Control and Emergent Metacognition Scales. This happened only for Emergent Metacognition for the non-

ADHD group. Despite that, differences were not significant and both groups had at least 70.83% of their children with a performance considered to be in the normal range. Although previous studies show that EFs deficits are present in ADHD and VP/VLBW patients, rating scales focus on a global and more nonspecific observation of executive functioning in the everyday context. They also depend on parent ratings, which might be biased by different development expectations (26)**.** This might have influenced our results, since our sample is characterized by a global developmental delay.

Overall, K-CPT 2 scores pointed to a higher number of participants in the clinical-suggestive range, with no significant differences between groups. Omissions, Commissions, Hit Reaction Time and Hit Reaction Time Block Change indicated that 26 to 67% of the children had a performance higher than one standard deviation from the normative mean, independent of group status. These measures are related to inattention, impulsivity, speed of processing, and vigilance - respectively. Specifically about Commissions, a measure related to impulsivity and inhibitory control, 38% of the ADHD group and 46% of the non-ADHD group fell in the clinical range, as suggested by the literature (10, 27).

Regarding reaction time variability (RTV), 76.2% to 100% of the sample showed an impaired performance and, again, no differences were found between groups. This variability is associated with most childhood psychiatric disorders, traumatic brain injury, dementia and aging populations (28, 27). Few studies investigated this issue in premature children. Adolescents born prematurely show an impairment in reaction time variability when compared to controls, but this impairment is milder than the one found in term-born ADHD adolescents (14). This result, however, was not observed in the same sample when another cognitive test was analyzed (29) **.** Although this construct still remains understudied in prematurity, it is well established that a higher than usual RTV is present in ADHD and is also a marker of general psychopathology (30, 28, 27). The pathophysiology of RTV is usually associated to abnormal frontal lobe volume and/or activation (28). Cortical maturation of the frontal lobe is delayed in ADHD children (31)**,** and a meta-analysis showed an overall reduction in brain volume, including white and gray matter in VP/VLBW school-aged children (32)**.** Specifically in

preschool children, a delay in normal cortical and surface development is associated to prematurity (33).

Another important aspect to discuss is that our sample was characterized by a below average mean IQ, independently of the group. However, this is not an unexpected finding since low birth weight is also associated with below-average IQ. The high degree of nervous system immaturity and the greater susceptibility to neonatal complications may lead to cognitive impairment. The cerebral networks of children with low birth weight are less connected, with lower brain volumes and lower cortical surface area, which might result in impaired cognitive functions (02, 34). In addition, results of a meta-analysis also showed that ADHD is associated to lower overall cognitive ability when compared to healthy controls (35).

The nature of the relationship between intelligence and executive functions is still controversial (36). Although many variables are included in the broader concept of executive functions, they are actually separable to a certain degree and differently correlated to each other as well as to the many areas of the brain (37). Among all other executive functions, inhibition has been found to have a low correlation to IQ (38). The same conception is valid for RTV: although higher inconsistency is related to lower IQ, the variance explained by IQ is usually small (39). A recent meta-analysis showed evidence for a low to moderate correlation with matrix intelligence tests - which are less affected by cultural aspects (40). Taking that into account, the deficits found in our sample in inhibitory control and RTV may be only partially explained by the low IQ of the participants.

Our findings should be understood in the context of some limitations. Although our sample's low average IQ is frequent in VP/VLBW children and it might not fully explain our results, we cannot discard it as limitation. Further studies investigating average-IQ preterm/low-birth preschooler's performance might improve our understanding of the impact of ADHD in executive functions in this population. Additionally, our moderate sample size in both groups might have decreased the power to detect between-group differences. However, it is important to note that all between group ES were small for both BRIEF-P and K-CPT 2 scores. Furthermore, the absence

of a full-term control sample imposes limitations for our analyses, making us rely on normative data for comparisons.

CONCLUSIONS

This study provides evidence for deficits in the performance of inhibitory control tests in preschool children born VP and/or with VLBW. The presence of ADHD did not impose an extra burden for the child's tests performance. Parents' reports seem to present lower sensitivity to capture executive deficits in this population. Impairment in RTV, a more basic cognitive process, was found in most participants, independent of group status. Our findings suggest that either neuropsychological tasks and parent reports on EFs may not be sufficiently sensitive to differentiate between ADHD and non-ADHD in VP/VLBW preschool children, or that these children already have a level of impairment in executive functions that does not leave much more room for additional impairment. More large-scale studies investigating the nature and long-term effects of inhibitory control deficits in these vulnerable populations are needed.

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References

1. World Health Organization (WHO). Preterm birth. Retrieved from; 2017: http://www.who.int/mediacentre/factsheets/fs363/en/.

2. Glass H, Costarino TA, Stayer AS, Brett C, Cladis F and Davis JP. Outcomes for extremely premature infants. Anesthesia & Analgesia; 2015: 120(6): 1337–1351: doi: 10.1213/ANE.0000000000000705.

3. Aarnoudse-Moens H, Weisglas-Kuperus N, van Goudoever JB and Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics; 2009*:* 124, 717–728: doi: 10.1542/peds.2008-2816.

4. Zomignani AP, Zambelli HJL and Antonio MA. Desenvolvimento cerebral em recém-nascidos prematuros. Revista Paulista de Pediatria; 2009: 27(2): 198-203.

5. O´shea MT, Downey C and Kuban CK. Extreme prematurity and attention deficit: epidemiology and prevention. Frontiers in Human Neuroscience; 2013: *7*: 578: doi: 10.3389/fnhum.2013.00578

6. American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. Washington, DC: Author (5th ed.).

7. Lahey BB, Pelham WE, Loney J, Kipp H, Ehrhardt, A, Lee SS, et al. Three-year predictive validity of DSM-IV Attention Deficit Hyperactivity Disorder in children diagnosed at 4-6 years of age. American Journal of Psychiatry; 2004: *161*:2014–2020: doi: 10.1176/appi.ajp.161.11.2014.

8. Seidman JL. Neuropsychological functioning in people with ADHD across the lifespan. Clinical Psychology Review; 2006 26, 466–485: doi: 10.1016/j.cpr.2006.01.004

9. Breaux R, Griffith S and Harvey E. (2016). Preschool neuropsychological measures as predictors of later Attention Deficit Hyperactivity Disorder. Journal of Abnormal Child Psychology*; 2016: 44* (8):1455-1471: doi: 10.1007/s10802-0160140-1.

10. Pauli-Pott U and Becker K. Neuropsychological basic deficits in preschoolers at risk for ADHD: a meta-analysis. Clinical Psychology Review; 2011: 31(4):626-37: doi: 10.1016/j.cpr.2011.02.005.

11. Jacobson LA, Crocetti D, Dirlikov B, Slifer K, Denckla MB, Mostofsky SH et al. Anomalous brain development is evident in preschoolers with Attention-Deficit/Hyperactivity Disorder. Journal of the International Neuropsychological Society; 2018*: 26*:1-9: doi: 10.1017/S1355617718000103

12. Çak TH, Kültür ÇES, Gökler B, Öktem F and Taskıran S. The Behavior Rating Inventory of Executive Function and Continuous Performance Test in preschoolers with Attention Deficit Hyperactivity Disorder. Psychiatry Investigation; 2017: *14*(3):260-270: doi: 10.4306/pi.2017.14.3.260.

13. Zhang HF, Shuai L, Zhang JS, Wang YF, Lu TF, Tan X et al. Neuropsychological profile related with executive function of Chinese preschoolers with Attention Deficit/Hyperactivity Disorder: neuropsychological measures and Behavior Rating Scale of Executive Function - Preschool Version. Chinese Medical Journal (English); 2018: 20; 131(6):648-656: doi: 10.4103/0366-6999.226893

14. James SN, Rommel AS, Cheung C, McLoughlin G, Brandeis D, Banaschewski T et al. Association of preterm birth with ADHD-like cognitive impairments and additional subtle impairments in attention and arousal malleability. Psychological Medicine; 2017: 2, 1-13: doi: 10.1017/S0033291717002963.

15. Potgieter S, Vervisch J and Lagae, L. Event related potentials during attention tasks in VLBW children with and without Attention Deficit Disorder. Clinical Neurophysiology; 2003: 114(10):1841-9.

16. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (KSADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry; 1997: 36:980–988: doi: 10.1097/00004583-199707000-00021

17. Kaufman S. A short form of the Wechsler Preschool and Primary Scale of Intelligence. Journal of Consulting and Clinical Psychology; 1972: 39(3), 361369.

18. Wechsler D. WPPSI-R – Wechsler Preschool and Primary Scale of Intelligence – Revised. San Antonio: The Psychological Corporation; 1989.

19. Conners CK. Conners' Kiddie Continuous Performance Test for Windows [computer program]. Toronto: Multi-Health; 2000.

20. Gioia GA, Espy KA and Isquith PK. Behavior rating inventory of executive function - preschool version. Lutz, FL: Psychological Assessment Resources; 2003.

21. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, N.J.: L. Erlbaum Associates; 1988.

22. Miranda M, Sinnes E, Pompeia S and Bueno O.O K-CPT em uma amostra brasileira: descrição do desempenho e comparação com as normas norte-americanas. Revista de Psiquiatria do Rio Grande do Sul; 2009: 31- 1.

23. Jaekel J, Eryigit-Madzwamuse S and Wolke D. Preterm toddlers' inhibitory control abilities predict attention regulation and academic achievement at age 8 years. The Journal of Pediatrics; 2016: 169, 87–92, 1: doi: 10.1016/j.jpeds.2015.10.029.

24. Barkley RA and Murphy KR. Impairment in occupational functioning and adult ADHD: the predictive utility of executive function (EF) ratings versus EF tests. Archives of Clinical Neuropsychology; 2010: 25(3):157-73: doi: 10.1093/arclin/acq014.

25. Sjöwall D and Thorell LB. A critical appraisal of the role of neuropsychological deficits in preschool ADHD. Child Neuropsychology; 2018: 14:1-21: doi: 10.1080/09297049.2018.1447096

26. Isquith PK, Crawford JS, Espy KA and Gioia GA. Assessment of executive function in preschool-aged children. Mental Retardation and Developmental Disabilities Research Reviews; 2005:11(3):209-15: doi: 10.1002/mrdd.20075.

27. Willcutt GE, Sonuga-Barke JSE, Nigg TJ and Sergeant AJ. Recent developments in neuropsychological models of childhood psychiatric disorders. Biological Child Psychiatry: Recent Trends and Developments; 2008: 24, 195–226 :doi.org/10.1159/000118526.

28. Tamm L, Narad ME, Antonini TN, O'Brien KM, Hawk LW and Epstein JN. Reaction time variability in ADHD: a review. Neurotherapeutics; 2012: 9 (3):500-8: doi: 10.1007/s13311-012-0138-5.

29. Rommel AS, James SN, McLoughlin G, Brandeis D, Banaschewski T, Asherson Pet al. Association of preterm birth with Attention-Deficit/Hyperactivity Disorder–like and wider-ranging neurophysiological impairments of attention and inhibition. Journal of the American Academy of Child and Adolescent Psychiatry; 2012: 56(1):40–50.

30. Kofler MJ, Rapport MD, Sarver DE, Raike JS, Orban SA, Friedman LM et al. Reaction time variability in ADHD: a meta-analytic review of 319 studies. Clinical Psychology Review; 2013: 33(6):795-811: doi:10.1016/j.cpr.2013.06.001.

31. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the National Academy of Sciences of the United States of America; 2007: 4; 104(49):19649-54: doi: 10.1073/pnas.0707741104.

32. Kieviet JF, Zoetebier L, van Elburg RM, Vermeulen RJ and Oosterlaan, J. Brain development of very preterm and very low-birthweight children in childhood and adolescence: a meta-analysis. Developmental Medicine & Child Neurology; 2012: 54(4):313-23: doi: 10.1111/j.1469-8749.2011.04216.x.

33. Phillips J, Montague E, Aragon M, Lowe J, Schrader R, Ohls R et al. Prematurity affects cortical maturation in early childhood. Pediatric Neurology; 2011: 45(4): 213–219: doi: 10.1016/j.pediatrneurol.2011.06.001.

34. Gu H, Wang L, Liu L, Luo X, Wang J,, Li, J., Liu, G., Hou F et al. A gradient relationship between low birth weight and IQ: a meta-analysis. Scientific Reports;2017: 7: 18035: doi:10.1038/s41598-017-18234-9.

35. Frazier TW, Demaree HA and Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in Attention-Deficit/Hyperactivity Disorder. Neuropsychology; 2004: 18(3):543-55: doi: 10.1037/0894-4105.18.3.543.

36. García-Molina A, Tirapu-Ustárroz J, Luna-Lario P, Ibáñez J and Duque P. Are intelligence and executive functions the same thing? Revista de Neurologia; 2010: 16, 50(12):738-46. Retrieved in: http://europepmc.org

37. Royall DR, Lauterbach EC, Cummings JL, Reeve A, Rummans TA, Kaufer DI et al. Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. Journal of neuropsychiatry and clinical neurosciences; 2002: 14(4):377-405. doi: 10.1176/jnp.14.4.377.

38. Friedman PN, Miyake A, Corley PR, Young ES, DeFries CJ and Hewitt KJ. Not all executive functions are related to intelligence. Psychological Science; 2006:17(2):172-9: do10.1111/j.1467-9280.2006.01681.xi.

39. Jensen RA. (1992). The importance of intraindividual variation in reaction time. Personality and Individual Differences; 1992: 13, (8)869-881: doi: https://doi.org/10.1016/0191-8869(92)90004-9

40. Doebler P and Sheffler B. The relationship of choice reaction time variability and intelligence: a meta-analysis. Learning and Individual Differences; 2016: 52s, 157166: doi: https://doi.org/10.1016/j.lindif.2015.02.009.

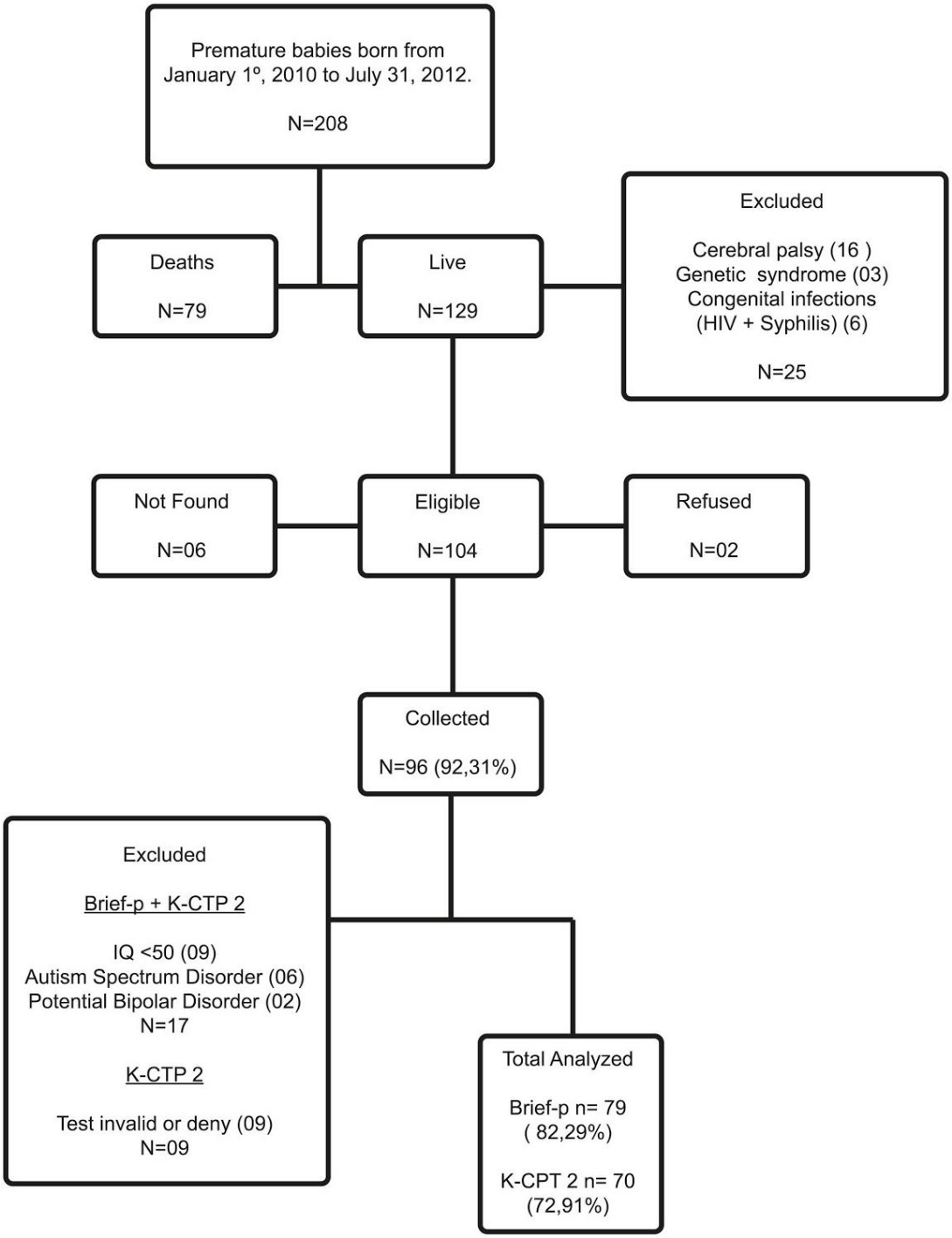

FIGURE 1: Sample selection flowchart.

TABLE 1: Sample Description.

	BRIEF-P (n=79)			K-CPT 2 (n=70)		
	ADHD (n=24)	non-ADHD (n=55)		ADHD (n=21)	non-ADHD (n=49)	
	mean (SD)	mean (SD)	p-value	mean (SD)	mean (SD)	p-value
Age (years)	5.58 (0.92)	5.46 (0.72)	0.257	5.81 (0.90)	5.48 (0.73)	0.114
IQ	69.88 (15.87)	76.64 (17.20)	0.104	70.52 (16,58)	78.04 (17.44)	0.098
Gestational age (weeks)	30 (2.53)	30.27 (2.49)	0.678	30.11 (2.68)	30.37 (2.42)	0.71
SES	24.08 (7.76)	26.40 (7.57)	0.218	23.90 (7.58)	26.57 (7.53)	0.18
	Frequency (%)	Frequency (%)	p-value	Frequency (%)	Frequency (%)	p-value
Gender (male)	12 (50%)	26 (47,27%)	0.823	11 (52.38%)	22 (44.90%)	0.565
ODD	11 (45,83%)	6 (10,90%)	0.001	6 (28.57%)	9 (18.37%)	0.004
Any Anxiety Disorder	7 (29,17%)	13 (23.64%)	0.603	5 (23.81%)	13 (26.53%)	0.811

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; SD, Standard Deviation; IQ, Intelligence Quotient; SES, Socioeconomic Status (higher is better); ODD, Oppositional Defiant Disorder.

TABLE 2: ADHD vs non-ADHD performance in Executive Function measures.

	ADHD	Non-ADHD		
	mean (SE)	mean (SE)	p-value	ES
BRIEF-P*	**(n=24)**	**(n=55)**		
Inhibitory Self-Control	40.13 (1.87)	35.46 (1.62)	0.062	0.046
Flexibility	26.6 (1.38)	26.32 (1.2)	0.88	0.001
Emergent Metacognition	40.60 (2.01)	39.72 (1.74)	0.74	0.002
K-CPT 2*	**(n=21)**	**(n=49)**		
Omissions	40.58 (7.21)	36.29 (5.78)	0.637	0.004
Commissions	104.69 (10.86)	103.03 (8.70)	0.903	0.001
Perseverations	7.18 (2.43)	8.89 (1.95)	0.576	0.005
HRT	726.37 (38.11)	693.73 (30.56)	0.496	0.007
HRT SD	374.32 (27.58)	361.91 (22.11)	0.72	0.002
Variability	112.66 (12.48)	127.74 (9.99)	0.336	0.017
HRT Block Change	-0.960 (9.39)	12.48 (7.77)	0.264	0.02
HRT ISI	112.30 (21.68)	77.78 (17.39)	0.208	0.025

*Potential confounders: age, estimated IQ, Oppositional Defiant Disorder; all measures are raw scores.

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; ES, effect size; BRIEF-P, Behavior Rating Inventory of Executive Function - Preschool Version; K-CPT 2, Conners' Kiddie Continuous Performance Test; HRT, hit reaction time; HRT SD, hit reaction time standard deviation; HRT Block Change, Hit Reaction Time Block Change; HRT ISI, Hit Reaction Time Interstimulus-Interval.

TABLE 3: Executive Function deficits in ADHD vs non-ADHD children.

	ADHD		non-ADHD		
	>1SD	**≤1SD**	**>1SD**	**≤1SD**	**p-value**
BRIEF-P	**n=24**		**n=55**		
Inhibitory Self-Control	6 (25%)	18 (75%)	6 (10.91%)	49 (89.09%)	0.109
Flexibility	1 (4.17 %)	23 (95.83%)	5 (9.09%)	50 (90.91%)	0.447
Emergent Metacognition	7 (29.17%)	17 (70.83%)	10 (18.18%)	45 (81.81%)	0.275
K-CPT2	**n=21**		**n=49**		
Omissions	12 (57.14%)	9 (42.86%)	26 (53.06%)	23 (46.93%)	0.753
Commissions	8 (38.1%)	13 (61.90%)	23 (46.94%)	26 (53.06%)	0.495
Perseverations	5 (23.81%)	16 (76.19%)	10 (20.41%)	39 (79.60%)	0.751
HRT	7 (33.33%)	14 (66.67%)	13 (26.53%)	36 (73.47%)	0.564
HRT SD	20 (95.24%)	1 (4.76%)	49 (100%)	0 (0%)	0.124
Variability	17 (80.95%)	4 (19.05%)	43 (87.76%)	6 (12.24%)	0.456
HRT Block Change	9 (42.86%)	12 (57.14%)	33 (67.35%)	16 (32.65%)	0.055
HRT ISI	16 (76.2%)	5 (23.81%)	39 (79.6%)	10 (20.41%)	0.751

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; SD, Standard Deviation; HRT, Hit Reaction Time; HRT SD, Hit Reaction Time Standard Deviation; HRT Block Change, Hit Reaction Time Block Change; Hit Reaction Time Interstimulus Interval.

9.3 TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Estamos convidando você e a criança pela qual você é responsável a participar da pesquisa "Fatores de Risco Para Transtorno de Déficit de Atenção/Hiperatividade em Crianças Muito Prematuras e/ou com Muito Baixo Peso ao Nascer" desenvolvido pelo Programa de Transtorno de Déficit de Atenção/Hiperatividade (ProDAH) e pelo Serviço de Neonatologia do Hospital de Clínicas de Porto Alegre (HCPA).

O Transtorno de Déficit de Atenção/Hiperatividade (TDAH) é uma condição psiquiátrica que afeta crianças, adolescentes e adultos, e tem como características principais um excesso de hiperatividade e impulsividade, e dificuldade em manter a atenção durante as atividades diárias. Se não diagnosticado e tratado adequadamente, o TDAH pode causar prejuízos no convívio familiar/social, e fraco desempenho escolar e profissional.

Crianças que nasceram prematuras, ou seja, antes do tempo esperado para uma gestação normal, tem mais chances de desenvolver o TDAH no futuro quando comparadas a crianças que nasceram na idade gestacional esperada. Entretanto, ainda não está bem estabelecido quais são as características que a criança que nasceu prematura apresenta e que a fazem desenvolver o TDAH.

Nosso objetivo é criar um escore de avaliação que ajude pediatras a identificar, entre crianças que nasceram muito prematuras (com menos de 32 semanas de gestação) e/ou de muito baixo peso ao nascer (menos de 1,5 Kg), aquelas que apresentam risco maior de desenvolver TDAH no futuro, buscando assim uma triagem precoce dessa doença.

Ao aceitarem participar do estudo, a criança pela qual você é responsável será avaliada por um psiquiatra especialista em infância e adolescência. A avaliação consiste em uma entrevista psiquiátrica, onde serão feitas perguntas e preenchidos questionários a respeito do comportamento da criança com o objetivo de avaliar os sintomas atencionais, de hiperatividade e impulsividade. Também será fornecido um questionário a ser entregue e preenchido pelo professor da escola de educação infantil, pré-escola ou escola no caso de a criança pela qual você é responsável estar frequentando esses locais. Também acessaremos dados da criança já coletados

previamente, durante o nascimento e internação hospitalar, tais como idade gestacional, peso ao nascimento, problemas de saúde na internação neonatal, exames de neuroimagem, informações da mãe como idade, nível sócio econômico, escolaridade e história familiar TDAH.

Havendo um diagnóstico positivo de TDAH, o médico da equipe irá explicar a doença e irá sugerir quais os encaminhamentos necessários para o tratamento da condição na rede pública.

As avaliações serão realizadas no Centro de Pesquisa Clínica do HCPA, terão duração de aproximadamente uma hora e meia e ocorrerão na seguinte ordem: consulta atual (hoje), consulta complementar, se necessário de acordo com o tempo que leva para responder aos questionários e consulta de devolução dos resultados de nossas avaliações onde forneceremos um resumo das avaliações que poderão ser entregues ao médico assistente do indivíduo. Em cada uma das avaliações o paciente será atendido por um médico psiquiatra especialista em infância e adolescência.

Para este estudo não são conhecidos riscos associados aos procedimentos previstos. Pode haver algum desconforto a você ou a criança ao responder a algumas perguntas pessoais, sendo que é possível interromper a participação a qualquer momento. Como benefício aos participantes, você também receberá uma avaliação psiquiátrica realizada por uma equipe com ampla experiência na saúde mental, sobretudo o TDAH em crianças e adolescentes, tendo a possibilidade de identificar alguns sintomas ainda não identificados. O estudo também contribuirá para o aumento do conhecimento sobre o assunto estudado e os resultados poderão auxiliar a realização de estudos futuros.

A sua participação e da criança pela qual você é responsável é totalmente voluntária e você pode desistir quando desejar. Você tem o direito de não participar desta pesquisa. A não participação ou desistência após ingressar no estudo não implicará em nenhum tipo de prejuízo de qualquer natureza ao paciente e/ou seus familiares. A participação no estudo não implicará em nenhum tipo de avaliação curricular. A recusa em participar ou a desistência da participação ao longo do estudo não acarretará nenhum prejuízo ao vínculo com a instituição.

Não está previsto nenhum tipo de pagamento pela participação no estudo e o participante não terá nenhum custo com respeito aos procedimentos envolvidos. A equipe se responsabiliza em fornecer passagem de ônibus para a criança e um adulto responsável acompanhante, ida e volta para aqueles indivíduos residentes em Porto Alegre.

Os pesquisadores se comprometem em manter a confidencialidade dos seus dados de identificação pessoal e os resultados serão divulgados de maneira agrupada, sem a identificação dos indivíduos que participaram do estudo.

Todas as dúvidas poderão ser esclarecidas antes e durante o curso da pesquisa através do contato com o Dr. Adelar Pedro Franz ou com o pesquisador responsável, Dr. Luis Augusto Rohde, pelo telefone 51-3359-8094 (horário comercial), ou 51-3359-8272 todas as sextas-feiras das 13:30h às 16:30h. Se desejar esclarecimentos quanto a questões de ética em pesquisa, o Comitê de Ética em Pesquisa poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227, ou através do telefone 33597640, das 8h às 17h, de segunda à sexta. Este documento será elaborado em duas vias, sendo uma delas entregue ao participante e outra mantida pelo grupo de pesquisadores.

Entendi as informações prestadas, tive a oportunidade de esclarecer minhas dúvidas e declaro estar de acordo com a participação neste estudo.

Nome completo da criança: _____

Nome completo do responsável: _____

Assinatura do responsável: _____

Nome do pesquisador: _____

Assinatura do pesquisador: _____

Porto Alegre, _____/_____/_____.

9.4 ADULT ADHD SELF REPORT SCALE

Responda a todas as perguntas abaixo. Marque um X no espaço que melhor descreve você nos últimos 6 meses (só marque 1 resposta em cada linha).	**Nunca**	**Raramente**	**Algumas vezes**	**Frequentemente**	**Muito frequentemente**
1. Com que frequência você comete erros por falta de atenção quando tem de trabalhar num projeto chato ou difícil?	0	1	2	3	4
2. Com que frequência você tem dificuldade para manter a atenção quando está fazendo um trabalho chato ou repetitivo?	0	1	2	3	4
3. Com que frequência você tem dificuldade para se concentrar no que as pessoas dizem, mesmo quando elas estão falando diretamente com você?	0	1	2	3	4
4. Com que frequência você deixa um projeto pela metade depois de já ter feito as partes mais difíceis?	0	1	2	3	4
5. Com que frequência você tem dificuldade para fazer um trabalho que exige organização?	0	1	2	3	4
6. Quando você precisa fazer algo que exige muita concentração, com que frequência você evita ou adia o início?	0	1	2	3	4
7. Com que frequência você coloca as coisas fora do lugar ou tem de dificuldade de encontrar as coisas em casa ou no trabalho?	0	1	2	3	4
8. Com que frequência você se distrai com atividades ou barulho a sua volta?	0	1	2	3	4
9. Com que frequência você tem dificuldade para lembrar de compromissos ou obrigações?	0	1	2	3	4
PARTE A – TOTAL					
1. Com que frequência você fica se mexendo na cadeira ou balançando as mãos ou os pés quando precisa ficar sentado (a) por muito tempo?	0	1	2	3	4
2. Com que frequência você se levanta da cadeira em reuniões ou em outras situações onde deveria ficar sentado (a)?	0	1	2	3	4
3. Com que frequência você se sente inquieto (a) ou agitado (a)?	0	1	2	3	4
4. Com que frequência você tem dificuldade para sossegar e relaxar quando tem tempo livre para você?	0	1	2	3	4
5. Com que frequência você se sente ativo (a) demais e necessitando fazer coisas, como se estivesse “com um motor ligado”?	0	1	2	3	4
6. Com que frequência você se pega falando demais em situações sociais?	0	1	2	3	4
7. Quando você está conversando, com que frequência você se pega terminando as frases das pessoas antes delas?	0	1	2	3	4
8. Com que frequência você tem dificuldade para esperar nas situações onde cada um tem a sua vez?	0	1	2	3	4
9. Com que frequência você interrompe os outros quando eles estão ocupados?	0	1	2	3	4
PARTE B – TOTAL					
SOMA TOTAL (PARTE A + PARTE B)					